STUDY OF CORRELATION BETWEEN P WAVE VERTICAL AXIS AND COPD SEVERITY BY PULMONARY FUNCTION TEST

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Certificate from the DEAN

This is to certify that this dissertation entitled **"STUDY OF CORRELATION BETWEEN P WAVE VERTICAL AXIS AND COPD SEVERITY BY PULMONARY FUNCTION TEST"** is the bonafide work of **Dr S.S.SRINIVASAN..,** in partial fulfillment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for **M.D General Medicine Branch I** examination to be held in **April 2015.**

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I , DR S.S.SRINIVASAN , solemnly declare that this dissertation titled **"STUDY OF CORRELATION BETWEEN P WAVE VERTICAL AXIS AND COPD SEVERITY BY PULMONARY FUNCTION TEST"** is a bonafide record of work done by at the Department Of General Medicine , Government Rajaji Hospital , Madurai , under the guidance of

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This dissertation is submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai in partial fulfillment of the rules and regulations for the award of **M.D Degree General Medicine Branch- I**; examination to be held in **April 2015.**

Place: Madurai

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INTRODUCTION

In India, COPD is the second most common lung disorder after pulmonary tuberculosis. The disease frequently encountered in middle aged patients and also COPD increasing public importance around the world. Estimates suggest that COPD will rise from the 6^{th} to the 3^{rd} most common cause of death worldwide by 2020.

AIMS AND OBJECTIVES

To estimate P wave vertical axis and FEV1 in patients with features of COPD.

To study P wave vertical axis inversely correlating with FEV1.

TO analyse whether P wave vertical axis can be substitute for FEV1 in assessing the severity of COPD.

METHODS AND MATERIALS

The study is to be conducted on 100 patients of Government Rajaji Hospital, who are all attending internal medicine and thoracic medicine op with clinical features and ECG changes of COPD .inclusion criteria: Age >45 year, Normal sinus rhythm with ECG change , past medical history of COPD,Imaging studies with COPD changes, Pulmonary function tests with COPD changes. Exclusion criteria: Congenital heart disease ,valvular heart disease, Cardiomyopathy.

STUDY PROTOCOL

The design for study is Observational study done in the period of July 2014 to September 2014 with simple Statistical analysis and participants are Patients attending in medicine and thoracic medicine op with clinical features and ECG changes of COPD

RESULTS

Among 100 patients, 17 patients had P wave vertical axis of 65-75 degree,19 patients had p wave vertical axis of 71-75 degree,20 patients had P wave vertical axis 76-80 degree,44 had P wave vertical axis of >80 degree. P wave vertical axis>80 degree is superior to P wave vertical axis 75 -80 degree is correlating with COPD severity and statically significant as p value is < 0.005.

CONCLUSION

From our study we concluded that , increasing age is associated with severity of the disease .Males are more commonly affected then females because of smoking.occupational exposure to risk factors confounding the risk of developing the disease when associated with smoking. Incidence of pulmonary hypertension and right ventricular dilatation increase with increase in severity of the diseases. p wave vertical axis is directly proportional to severity of COPD and inversely correlating with the FEV1 of predicted .

KEY WORDS

Vertical P-wave axis, the electrocardiographic synonym for pulmonary emphysema, The electrocardiogram in pulmonar emphysema,electrocardiogram in chronic cor pulmonale,Pulmonary emphysema: classical, quasi-diagnostic ECG

HISTORICAL PERSPECTIVE

The beginning of modern chest medicine can be traced to the classic volume by Laennec, "A treatise on diseases of the chest" which appeared in 1821 laid the corner stone of modern chest medicine.

In his treatise, Laennec, devoted one chapter to "Pulmonary Catarrh or Bronchitis" and emphysema. The chapter on bronchitis distinguishes between acute and chronic form and sub divides chronic bronchitis into two types – the humid (Copious Expectoration) and dries (Scarcely any Expectoration). He identified "Dilatation of air cells" as the essential feature of emphysema.

Recognition of chronic bronchitis as a potentially grave illness rather than as a trivial but not disabling disease had to wait the "London Fog" of 1953, which was brought about by bad weather and air pollutants, carried with it a surge in morbidity and mortality due to chronic lung disease .

After World War II, clinical investigations of pulmonary disease were provided with a new diagnostic armamentarium; Pulmonary Function tests were extended beyond simple spirometry and innovative techniques were developed for assessing the distribution of gases within the lungs which greatly improved our understanding of COPD.

INTRODUCTION

In India, COPD is the second most common lung disorder after pulmonary tuberculosis. The disease frequently encountered in middle aged patients and also COPD increasing public importance around the world. Estimates suggest that COPD will rise from the 6th to the 3rd most common cause of death worldwide by 2020.

Emphysema of any pathogenesis nearly always due to chronic obstructive pulmonary disease and rarely due to alpha 1 antitrypsin deficiency produce a state of abnormal lung hyperinflation and has been shown to carry on association with a vertical frontal p wave axis.

Patients with COPD show that vertical p wave axis in ECG and forced expiratory volume in pulmonary function test were inversely correlating, so ECG can be used to assess the severity of COPD in place of pulmonary function test and also vertical P wave axis (>60) during a sinus rhythm can be easily detected by a simple glance at the electrocardiogram.

The present study is to compares the P wave vertical axis, which is reproducible, patient friendly, less procedure related complication, minimal time consuming against the more cumbersome method of FEV1 measurement in assessing the severity of COPD.

AIMS AND OBJECTIVES

1. To estimate P wave vertical axis and FEV1 in patients with features of COPD.

2. To study P wave vertical axis inversely correlating with FEV1.

3. TO analyse whether P wave vertical axis can be substitute for FEV1 in assessing the severity of COPD

REVIEW OF LITERATURE

DEFINITION

Chronic obstructive pulmonary disease is Characterised by persistent airflow limitation that is not fully Reversible, usually progressive and associated with a chronic Inflammatory response in the airway and the lung to noxious .

Particles or gases.

1. EMPHYSEMA

   Emphysema is defined as destruction and enlargement in The lung alveoli.

2. CHRONIC BRONCHITIS

   This condition associated with excessive mucous Production sufficient to cause cough with expectoration At least 3 months a year for more than 3 consecutive years

3. SMALL AIRWAY DISEASE

EMPHYSEMA

Types of emphysema

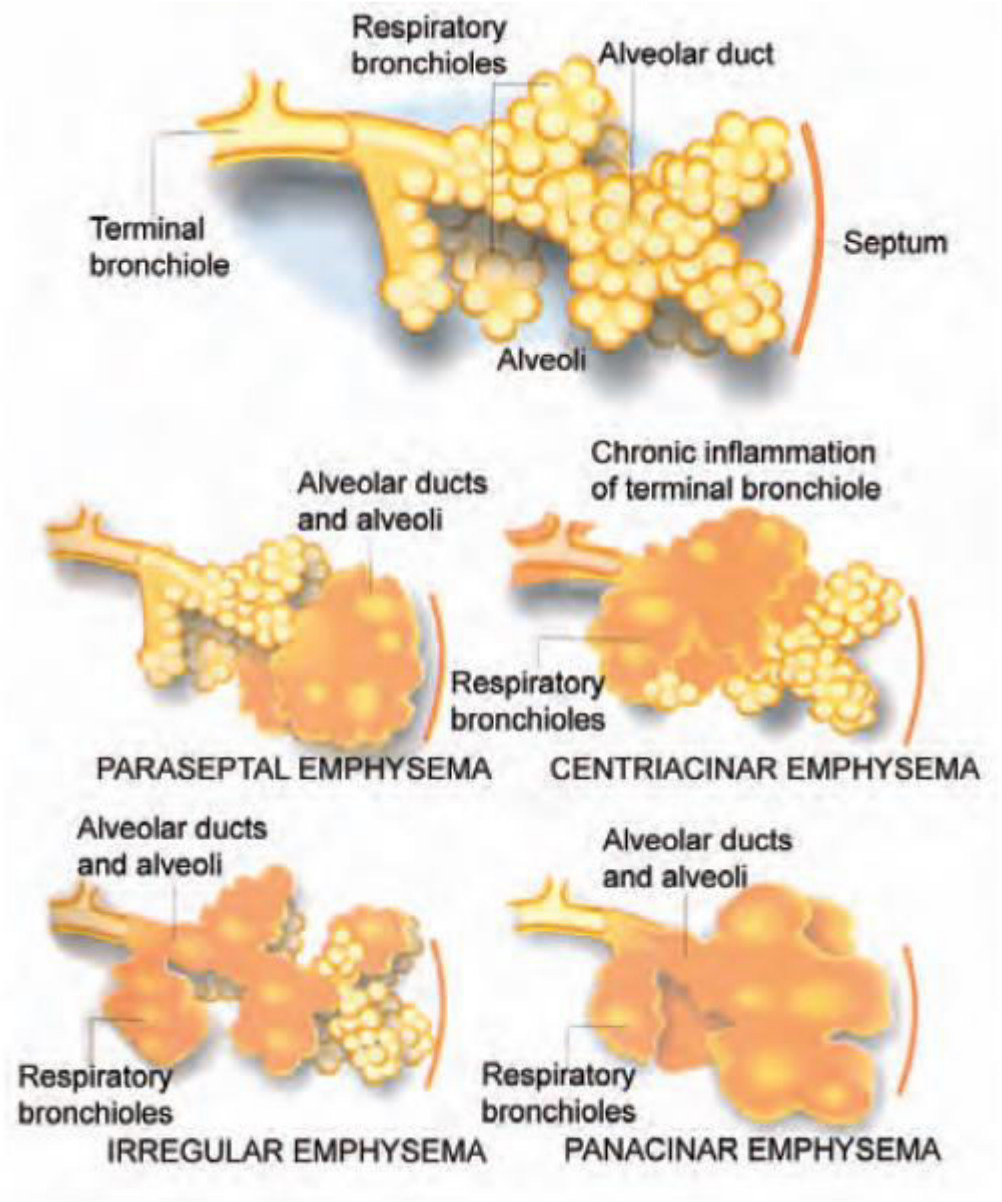


Fig. 4.30: Types of emphysema

Centriacinar emphysema: proximal portion of respiratory unit and central part are destructed and enlarged. Apices and upper lobes are predominantly involved. This predominantly seen in male patients with chronic bronchitis

Panacinar emphysema: these type of emphysema seen in alpha 1 antitrypsin deficiency individual.it is particularly involve lower lobes because lower lobes are rich in blood supply .protease rich enzymes are present in neutrophils that destruct the alveoli which is not able to inhibit by anti-protease enzymes in this individuals due to deficiency.

Paraseptal emphysema: this type of emphysema can lead to pneumothorax because its mainly found near to pleura. Distal acinus is predominantly involved.

Irregular emphysema: this could be seen in any type of emphysema.

SPECIAL VARITIES OF EMPHYSEMA

Compensatory emphysema: in response to pathology to same lung or opposite lung, normal lung become hyper inflate as a compensatory mechanism. Here the alveoli septea are not destroyed .clinically there is no signs of emphysema.

Mediastinal emphysema: this type of emphysema occurs due to rupture of over distended alveoli .this may occur in following condition

a.severe bronchial asthma

Rupture of emphysematous bulle

Rupture of oesophagus

Subcutaneous emphysema: this type of emphysema occur due to escaped air tracks up into the subcutaneous tissues of neck. If the COPD patient present with neck swelling, we have to think in terms of subcutaneous emphysema possibility.

CHRONIC BRONCHITIS

It is subdivided into

a.simple chronic bronchitis

b.chronic mucopurulent bronchitis

c.chronic bronchitis with obstruction

REID INDEX

Reid index is expressed as ratio of sub mucosal glands to that of bronchial wall.

In normal individuals, its 0.44±0.09

In chronic bronchitis, its 0.52±0.08

When the sub mucosal layer thickness >50% of bronchial wall thickness it is highly suggestive of chronic bronchitis .

DIFFERENTIATING FEATURE BETWEEN EMPHYSEMA AND CHRONIC BRONCHITIS

FEATURES	PREDOMINANT EMPHYSEMA (PINK PUFFER)	PREDOMINANT BRONCHITIS (BLUE BLOATER)
Age of onset	6^{th} decade	5^{th} decade
Cough	After dyspnoea	Before dyspnoea
Dyspnoea	Severe	Mild
Sputum	Scanty,mucoid	Copious, purulent
Infections	Less common	Common
Respiratory insufficiency	Often terminal	Repeated attacks
Chest x ray	Hyperinflation ± bullous changes; small heart	Increased bronchovascular markings; large heart
Paco2 (mm Hg)	35 – 40	50 – 60
Pao2 (mm Hg)	65 -70	45-60
Pulmonary hypertension	Mild	Moderate to severe

Cor pulmonale	Preterminal stage	Common
Diffusing capacity	Decreased	Normal to slight reduction
Lung compliance	Increased	Normal

GOLD CRITERIA FOR COPD SEVERITY

GOLD stage	Severity	Spirometry
I	Mild	$FEV_1/FVC < 0.70$
		$FEV_1 \geq 80\%$ predicted
II	Moderate	$FEV_1/FVC < 0.70$
		$50\% \leq FEV_1 < 80\%$ predicted
III	Severe	$FEV_1/FVC < 0.70$
		$30\% \leq FEV_1 < 50\%$ predicted
IV	Very severe	$FEV_1/FVC < 0.70$
		$FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted plus chronic respiratory failure

EPIDEMIOLOGY

COPD is expected to be the third most common cause of mortality and the fifth for loss of DALY worldwide according to Global Burden of disease study.

PREVALENCE IN INDIA

The exact prevalence in our country could not be ascertained because of misdiagnosis, underassessment, lag of extensive studies, poor statistical information. The prevalence rate varies from 2 to 22 per cent in males and 1.2 to 20 percentage in females. Recently ICMR has done the INSEARCH study in four cities and reported prevalence of 5% in males and 3.2% in females more than 35 years of age. The total population affected by the disease has increased to 14.84 million in 2011 from 6.45 million in 1971. In India the sex ratio and the smoker to non smoker ratio are not as high when compared to western statistics. The reason for disparity is biomas fuel combustion which is important risk factor in women more so in villages. Data on mortality statistics are limited; 7% mortality has been attributed to chronic respiratory illness.

RISK FACTORS INFLUENCING ONSET AND PROGRESSION

SMOKING

Tobacco smoking is the most important and the well-studied risk factor. About 85% of COPD is related to smoking. The remaining 15% is attributed to smoke from burning biomass fuels like woods, from occupational exposure to dust and smoke and cow dung for cooking.

The effect of smoking on decline lung function has been proved in many studies. cigarette smokers show high annual rate of decline in FEV1 of about 50 ml, this is nearly double the average value of 30 ml annually present in non-smokers .even though ,there is considerable variation in FEV1,with some smokers showing very rapid rate of decline. The decline in FEV1 might be faster in natural history of disease before COPD is established.

But still not all smoker developed the disease and even among those who smoke there are variations in response to the duration of smoking which suggest that other factors particularly environment modulate, the effect of smoking, content of smoke such as tar, nicotine ,other constituents and genetic in these patients.

Mortality due to COPD is twofold higher in smokers who smoke ≥ 25cigrattes per day then those with smoking fewer than 15 cigarettes per day

PASSIVE SMOKING

There is statistically significant correlation showed in relation with lung cancer in passive smokers .these is shown mainly in patients who are chronically exposed since childhood with significant lower of FEV1 in adulthood.

AIRWAY RESPONSIVENESS

Though the concept of airway hyper responsiveness is proved beyond doubt in bronchial asthma, in COPD there are conflicting reports even though there are recent studies supporting the airway hyper responsiveness in COPD patients.

RESPIRATORY INFECTIONS

Infections associated with risk

1. Childhood respiratory infections
2. Previous history of tuberculosis even when adequately treated with ATT.
3. Inadequately treated bronchial asthma

INDOOR AIR POLLUTIONS

Though in developed countries, smoking is the major risk factor, in developing countries like ours causes other than smoking contribute one third

to half of all cases. Among them chronic exposure to carbon monoxide, HCHO and nitric oxide and sulphur dioxide and others released from biomass fuel combustion is the important risk factor particularly in female patients.

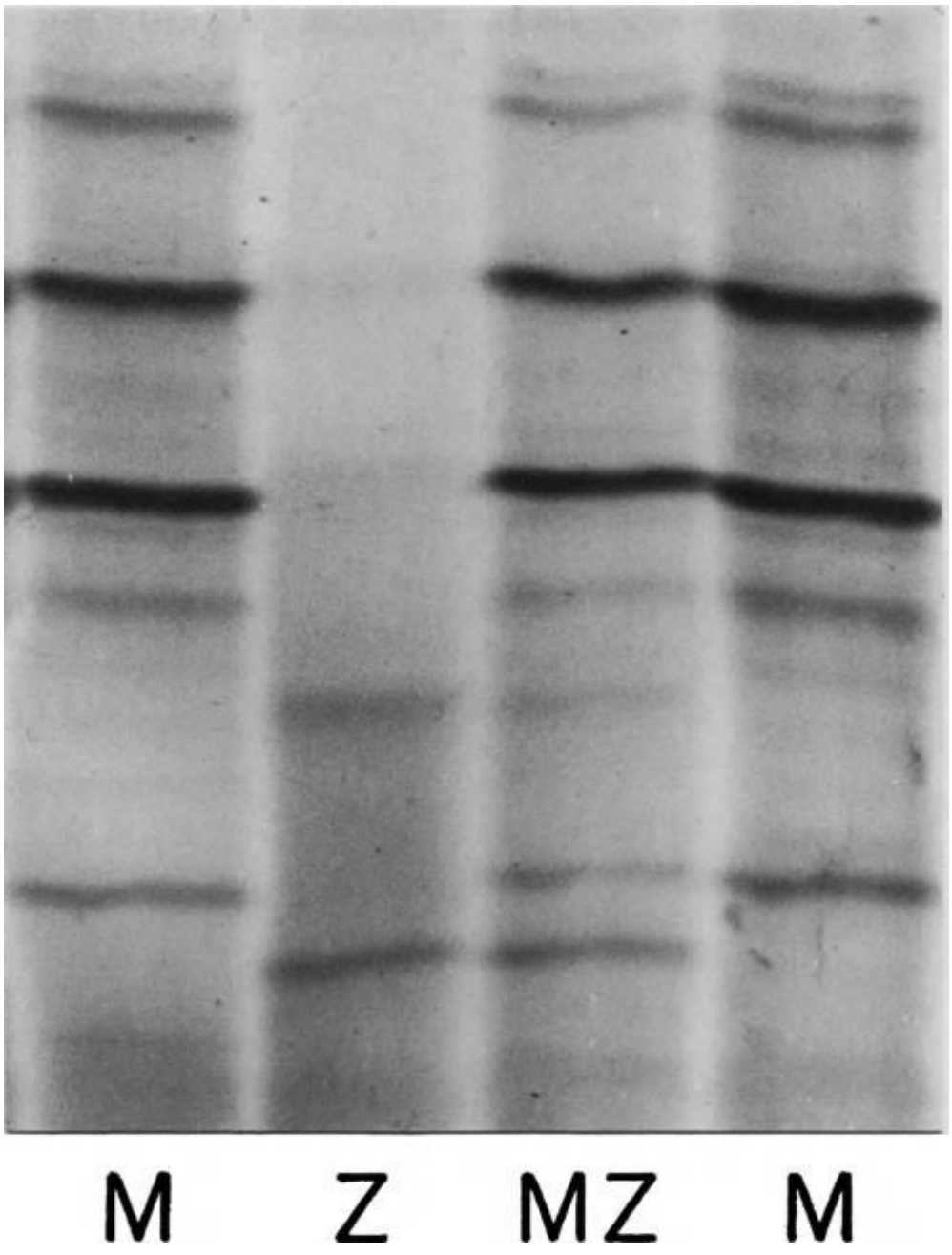
WHO identified that, if the sulphur dioxide level ≥150 microgram /m3 shows increased morbidity in terms of symptoms and hospital admissions in adult COPD.

Those who have poor cardiopulmonary reserve and elderly people show increased mortality if the sulphur dioxide level or black smoke ≥500microgram/m3

GENES

The difference in expression of disease among smokers could possibly be explained by the genetic factors. Alpha 1 antitrypsin deficiency due to alteration in SERPINA 1 locus encoding the enzyme is the only proven genetic factor related to the COPD.

Allele	Alpha 1 Anti trypsin
M	Normal
S	Slightly reduced
Z	Markedly reduced
Null	Absent



The above picture shows that pattern of PiM,PiZ and Pimz alpha 1 AT on isoelectric focus. Because of its multiheterogenisity ,it appear as multiple bands.PiM and PiZ shows different band patterns, while PiMZ shows combination of both PiM and PiZ.

One has to suspect alpha 1 antitrypsin deficiency as the cause in patients with

1. Age of onset <40 years of age
2. Insignificant history of smoking
3. Predominant lower lobe involvement.
4. Necrotizing panniculitis(weber Christian disesase)
5. C ANCA positive vasculitis (wegeners granulomatosis)
6. Early onset of emphysema in family members or non-smoking related emphysema.
7. Bronchiectasis without other aetiology

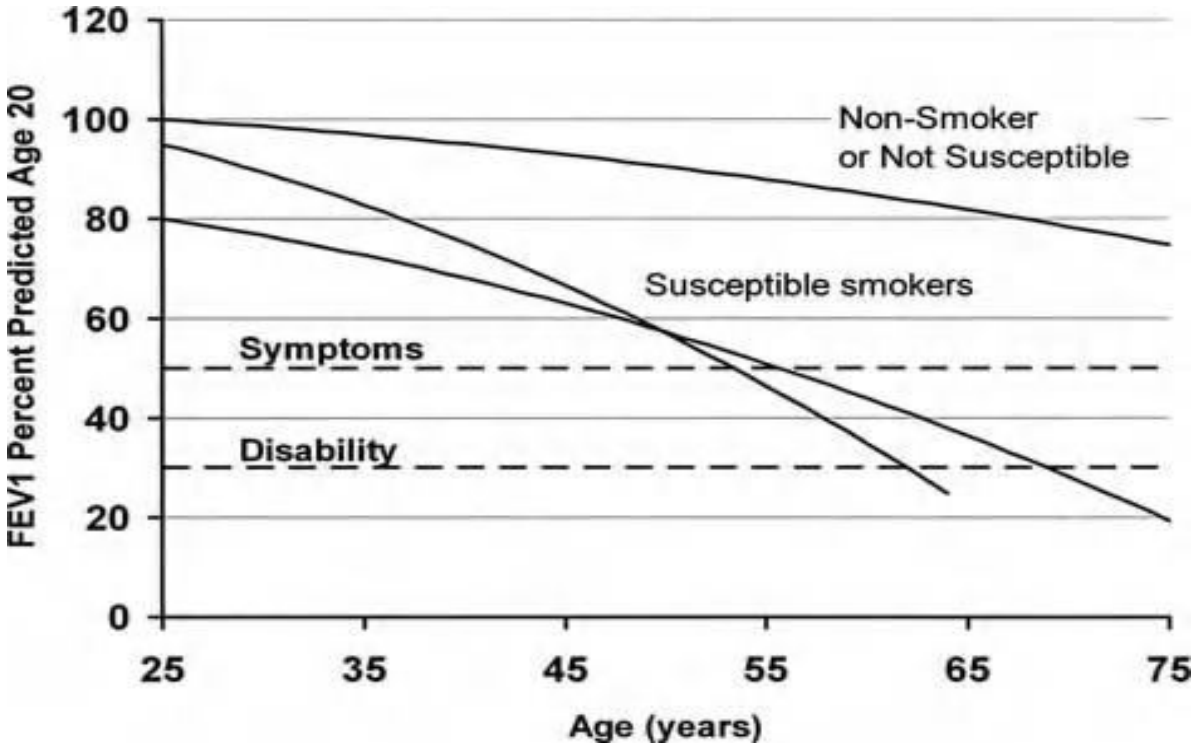
PiZZ is the most common form of severe alpha 1 antitrypsin deficiency showing greatly accelerated decline in FEV1 .

PiM is the commonest allele in all population and the most common genotype is PiMM.

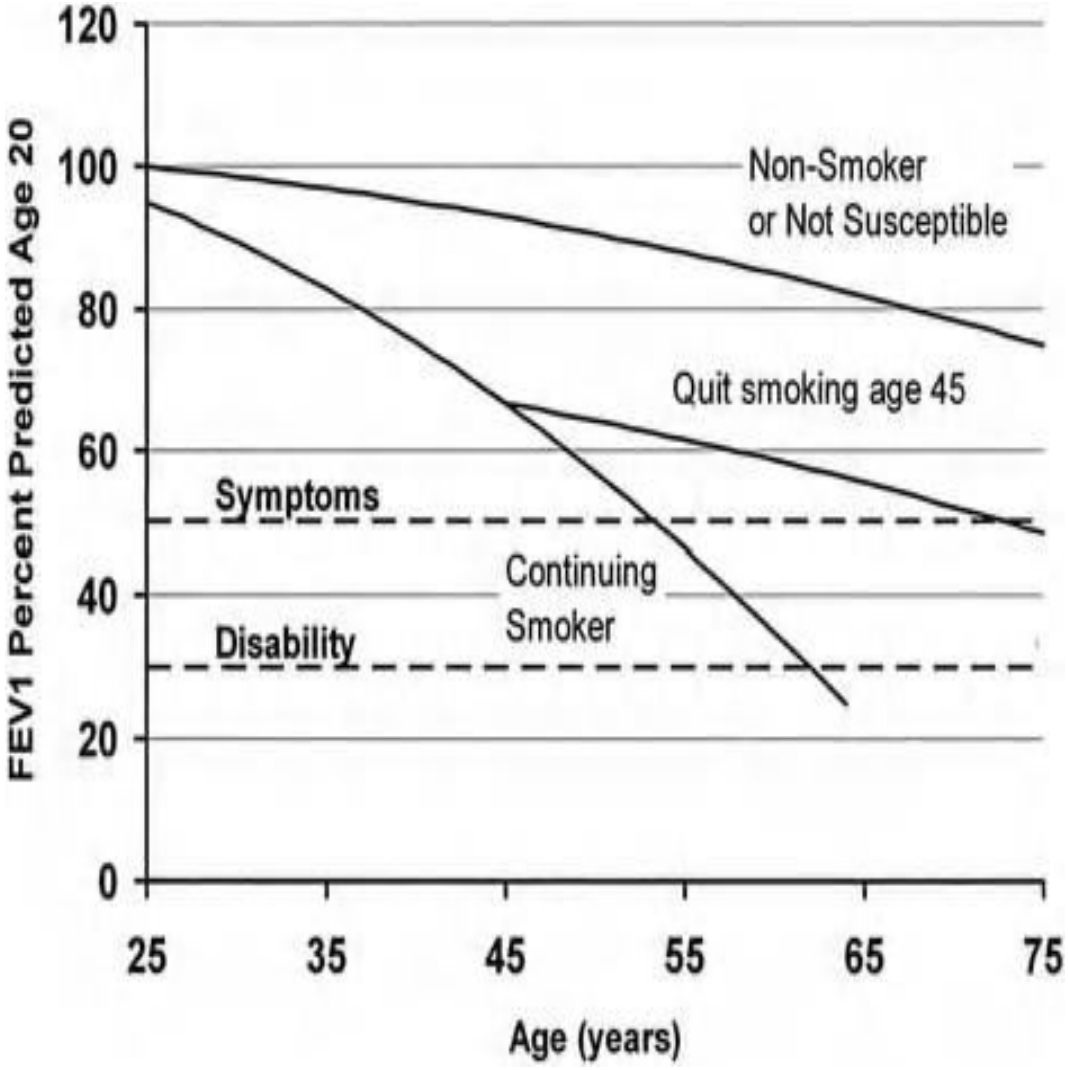
Treatment for this subset of individuals is weekly intravenous administration of alpha 1 antitrypsin.

AGE

Increasing age physiologically decreases the function of lung which may also contribute.



In vertical axis FEV1 plotted and horizontal axis age of the person is plotted. This shows that ,in non-smoker or not susceptible to smoking will lose 25% of his /her lung function throughout his life. Those who smoke or are susceptible to smoking will have decline in lung function rapidly as shown in this picture. Even though abnormal lung function is detected in these patients ,symptoms develop only when the lung function reduce to less than 50%



The above picture represents natural history of COPD with hypothetical case scenario who continues smoking upto the age of 45 years then he discontinues the smoking.here once the patient stops smoking before development of symptoms the lung fuction goes to normal range. Once the patient who is detected to have abnormal lung function before the development of symptoms cessation of smoking can revert the lung function to normal .

OCCUPATION

There is causal correlation between occupational dust exposure and development of mucus hyper secretion. Coal miner's shows development of small excess decline in FEV1 and increased mortality.

Those who are exposed to welding fumes are also showing development of COPD and workers who are exposed to cadmium also develop COPD in later days.

GENDER

In the past , the prevalence and mortality were more among men. As on date it is almost equal among men and women. When compared to men, women's susceptibility to the ill effects of tobacco smoking is significantly higher.

LUNG GROWTH AND DEVELOPMENT

The factors that affect the lung growth and development During the intrauterine life, and childhood increases an individual's susceptibility to develop COPD in the later years of life.

LOW SOCIOECONOMIC STATUS

The risk of developing COPD is inversely proportional to socioeconomic status

PATHOPHYSIOLOGY

Pathological changes in the lungs lead to corresponding physiological changes characteristic of the disease which occur in the following order:

Mucus hyper secretion

Ciliary dysfunction

Airflow limitation

Pulmonary hyperinflation

Gas exchange abnormalities

Pulmonary hypertension

Cor pulmonale

AIRFLOW LIMITATION

Airflow limitation due to decreased airway calibre and increased airway resistance, impaired elastic lung recoil during expiration manifest in spirometry as a reduction in the ratio of FEV1/FVC < 0.7 (FEV1- forced expiratory volume in 1 second, FVC- forced vital capacity) and reduced forced bronchodilator FEV1 predicted value is a cardinal feature for the disease diagnosis and dividing into stages.

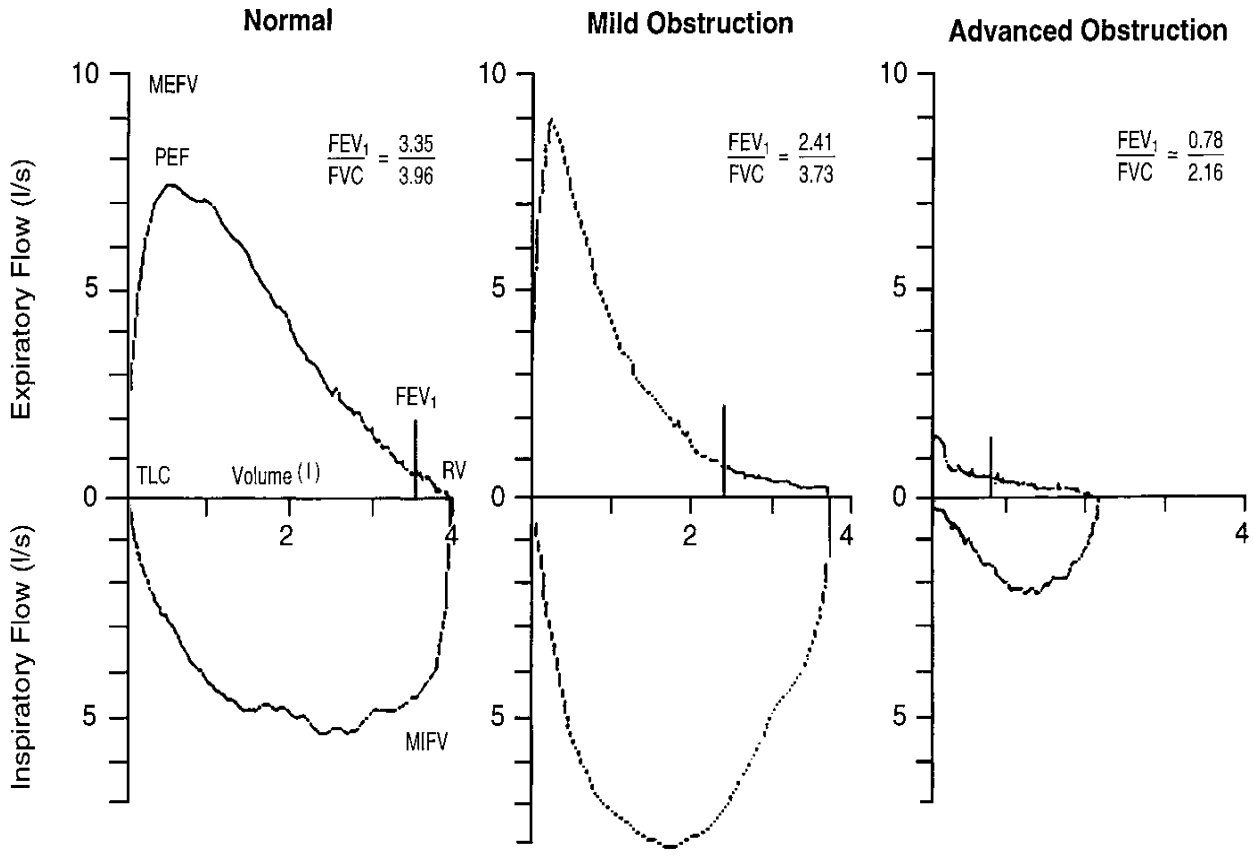
FVC at 6 seconds (FEV6) in patient with COPD is adequate and equivalent to FVC in individuals with severe obstruction.

During forced expiration there is airway instability and narrowing ,this the cause for discrepancies between inspiratory and expiratory flow.

From the flow pressure curve we can quantify the diminished elastic recoil and increased airway resistense by reduced maximal expiratory air flow.

Decreased elastic recoil shows –normal slope with premature termination.

Increased airway resistence shows –less steep slope



MEFV –maximum expiratory flow volume

MIFV-maximum inspiratory flow volume

LEFT-shows normal subject

MIDDLE-mild airway obstruction due to COPD

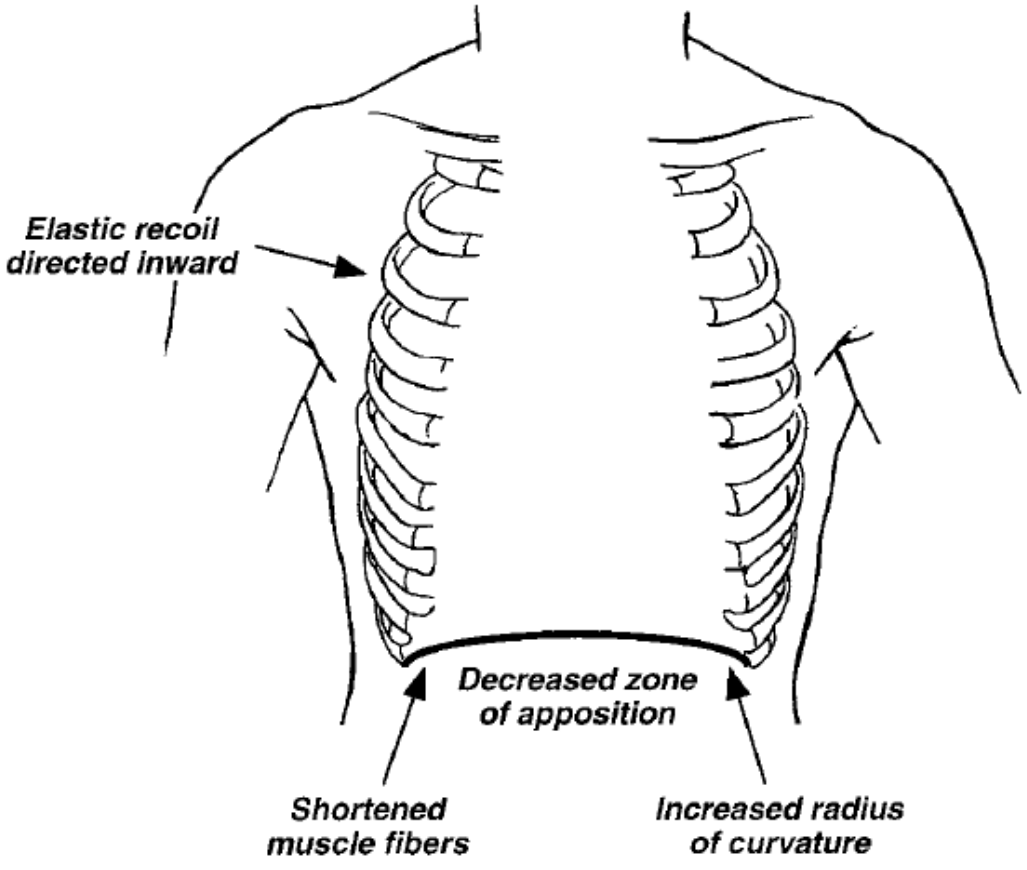
RIGHT-shows severe obstruction due to COPD

HYPERINFLATION

In COPD patients there is hyperinflation as shown by increased RV and increased ratio of RV/TLC and later increase in TLC. (RV- residual volume, TLC – total lung capacity)

Mechanism

The primary mechanism during expiration from small airways and alveoli is driven from the inward elastic recoil pressure of the lung which is also contributed by the counteracting thoracic wall outward pressure. At the end of tidal expiration both these balance each other resulting in particular amount of air remaining in the lungs named as FRC(Functional residual capacity). In COPD patients, due to destruction of lung parenchyma the inward pressures are low and it comes into equilibrium with the outward pressure at increased volumes of FRC resulting in hyperinflation



Hyperinflation may be an advantage as it favours conservation of maximum expiratory airflow by the following ways

1. Increase lung volume

2. Increase elastic recoil pressure

3. Enlarge airway lumen

4. Decrease airway resistance

However hyperinflation has untoward effects on mechanics of the thorax.

1. increase work of breathing

2. induce dyspnea

But hyperinflation of the lung keeps the diaphragm at a mechanical disadvantage i.e flattening of diaphragm resulting in functional diaphragmatic paralysis.this flatting of diaphragm leads to number of ill effects.those are

1. Because of loss of apposition zone between diaphragm and abdominal wall, during inspiration positive abdominal pressure not transmitted as virtually to chest. This leads to hampering rib cage movement and impairing inspiration.

2. Because of flatting of diaphragm muscle fibres are shorter than those of more normally curved diaphragm, this ultimately lead to less effective generation of inspiratory pressure.

Concurrent with hyperinflation, in patient with COPD inspiratory capacity also commonly reduced. This finding has prognostic significance that is independent of FEV1.

GAS EXCHANGE

The partial pressure of oxygen will be maintained until FEV1 s less than 50% of the predicted value and co2 retention will be observed only when the FEV1 is less than 25% of the predicted value. Gas exchange impairment in COPD is mainly due to the mismatch between the ventilation and perfusion. Large bullae will complicate this issue further because they are non-functioning airspaces with both poor perfusion and ventilation and moreover they occupy a significant volume of lung and hence compress and compromise the adjacent functional parenchyma.

V/Q MISMATCH

The characteristic feature of COPD is ventilation perfusion mismatch, this heterogeneous process affect not only the lung parenchyma but also affect the airways.

Ventilation – perfusion mismatching is the primary cause for the reduced Po2 that occur in COPD.From this view, modest increase in inhaled oxygen are effective in treatment of COPD.

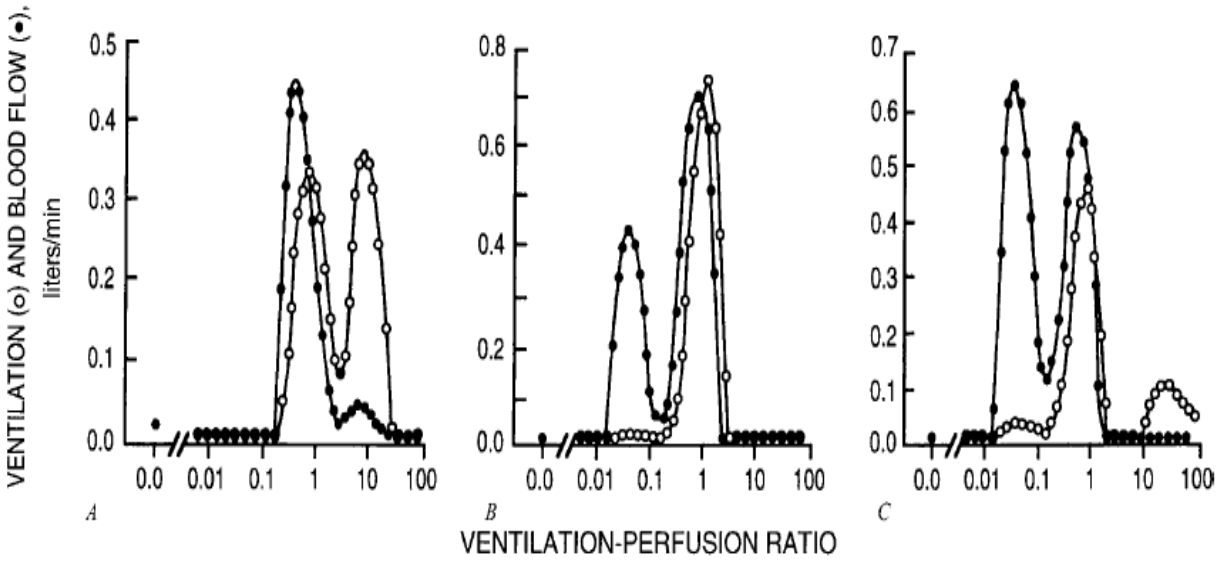


Figure 41-5 Ventilation-perfusion distributions in three persons with COPD determined by the multiple inert gas elimination technique (MIGET). *A*. Regions of high ventilation-perfusion characteristic of "emphysematous," type A COPD. *B*. Regions of low ventilation-perfusion characteristic of "chronic bronchitis," type B COPD. *C*. Regions of both high and low ventilation-perfusion characteristic of many people with COPD. In the normal person, not shown, ventilation-perfusion virtually overlaps and peaks at about a ventilation-perfusion ratio of 1. *(From Wagner PD, Dantzker DR, Dueck R, et al: Ventfl ation-perfusion inequality in chronic obstructive pulmonary disease. J Clin Invest 59:203–216, 1977, with permission.)*

DYSPNEA

Most of the COPD patient seek medical care only when they develop dyspnea.dyspnea impairs their day to day activites and affect the qualities of life.patient present with complaints of dypnea only when the FEV1 fall to <60% of expected.

The mechanism for breathlessness in COPD is +currently not well known. Neural signals pertaining to abnormalities of chest wall and airway mechanics seems to be important.

1.An increased feeling of expenditure relating to the pressure required from respiratory muscles relating to their maximum pressure generating capacity.

2.Impuse of "length-tension inappropriateness "from the respiratory muscles because of hyperinflation

3.Also,signals from airways leading abnormal dynamic compression during exhalation have been described.

4.except in acute scenario hypercarbia and hypoxia play little role in dyspnoea.

PATHOGENESIS

ACTIVATION OF MACROPHAGES

Macrophages are the cells found in the normal lower airways. Cigarette smoke contains oxidants which inactivates the histone deacetylase II with a resulting increase in acetylated chromatin thereby promoting increased transcription of pro inflammatory cytokines and matrix metalloproteinase. This pro inflammatory cytokines recruits neutrophils and stimulates neutrophil elastase. Macrophage secreted matrix metalloproteinase and neutrophil secreted elastase acts together and causes lung damage.

LOSS OF CILIA

Cigarette smoke causes loss of cilia in the airways and predispose to bacterial infection with neutrophilia.

ANTIELASTASE HYPOTHESIS

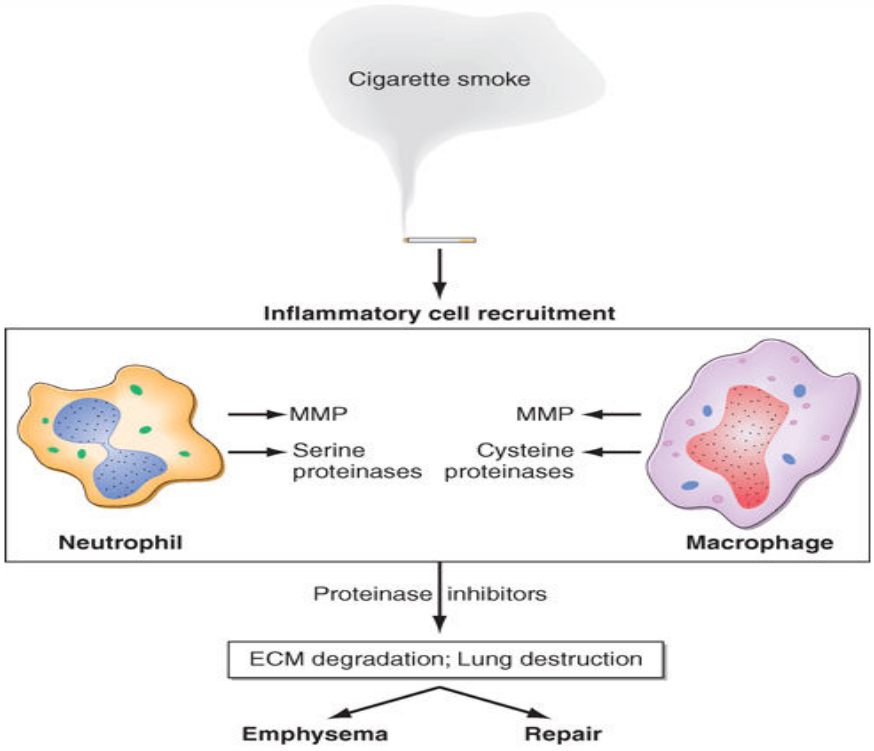
Alpha 1 anti trypsin deficiency

Neutrophils in the alveoli are stimulated by variable triggers which get activated and recruited and they release the granules such as proteinases, catapsins, elastase and matrix metalloproteinase and also reactive oxygen species which inhibit alpha 1 anti trypsin. Because of deficiency of alpha 1 anti trypsin , counteraction with granules released by neutrophis is decreased and this results in destruction of air spaces

SMOKING

In smokers both neutrophils and macrophages are increased in alveoli. Neutrophils upon activation release the above said proteases and activate macrophages release a variety of cytokines, ROS, chemokines and a variety of matrix mataloproteinases which are not inhibited by alpha 1 antitrypsin rather these enzymatically degrade alpha 1 antitrypsin and thus enhancing pulmonary destruction several fold. CD8 lymphocytes

increase apoptosis of alveoli and CD4 cells triggers autoimmunity against native lung tissue.



OXIDANT STRESS

The normal lung contains high amount of anti oxidants such as glutathione to handle the oxidant stress. Smoking activates inflammatory cells by the above said mechanism and releases free radicals which shift the balance towards oxidant stress which inactivates anti proteases

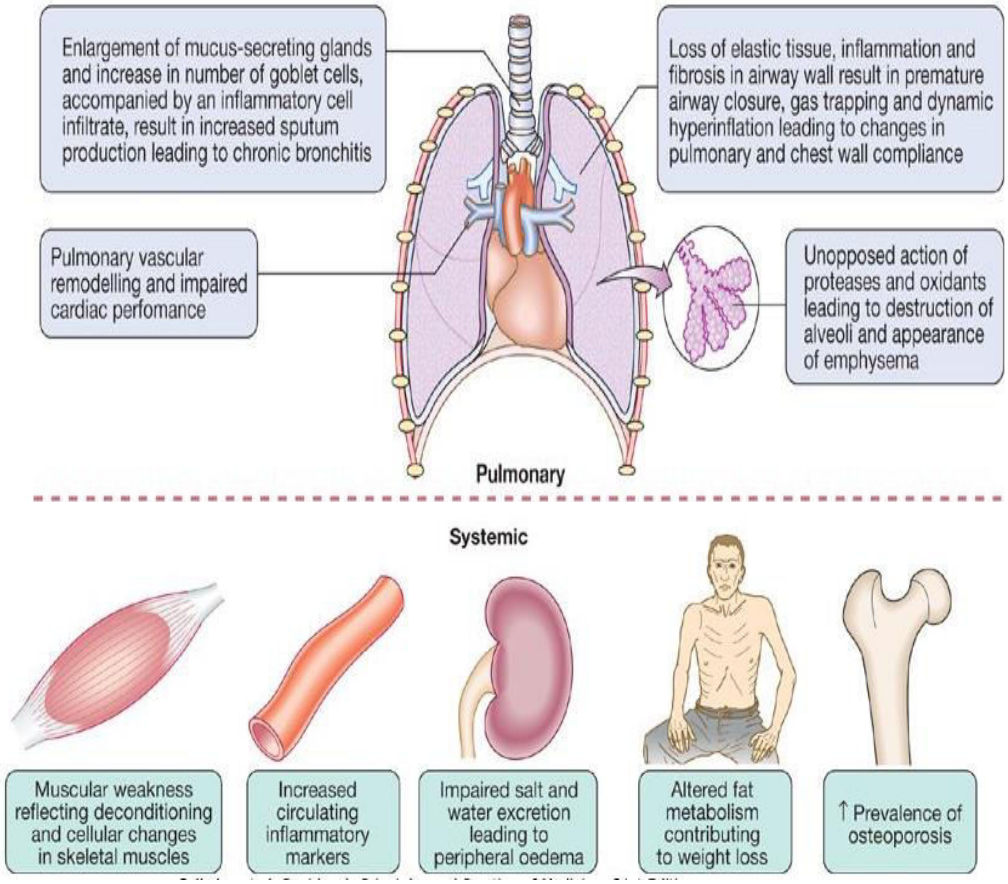
causing lung destruction in patients even with normal alpha 1 AT. Oxidant stress also result in loss of surfactant, reduction in elastin synthesis, Extra cellular matrix apoptosis.

CLINICAL PRESENTATION

HISTORY

SYMPTOMS

1. Chronic cough
2. Expectoration
3. Dyspnea on exertion, insidious in onset and gradually progressive over time. Sudden worsening of dyspnea could be either on due to exacerbation or pneumothorax or other complications.
4. Wheeze
5. Loss of weight – in severe disease (other causes should be ruled out before attributing it to the disease per se i.e. bronchogenic carcinoma)



SIGNS:

The physical examination might be completely normal in patients in the beginning stages till there is significant deterioration in pulmonary function.

GENERAL EXAMINATION

1. Stigmata of smoking – nicotine stains, etc.
2. Cyanosis may be present.
3. Clubbing is not a sign of disease per se and if clubbing is present one should search for carcinoma of lung.

4. Pedal edema, ascites, elevated JVP due to pulmonary hypertension and cor pulmonale.
5. Patient may have hypoxemia.

RESPIRATORY SYSTEM EXAMINATION

a. Patient with severe disease may have acting accessory muscles of respiration with the patient assuming "tripod" position to enhance the synergistic action of these muscles.
b. Hoover's sign – the movement of costal margins towards the midline during inspiration.
c. Signs of hyperinflation – barrel shaped chest, hyper resonance on percussion
d. On auscultation patient may have prolonged expiratory phase, diminished intensity of breath sounds, expiratory wheeze.
e. Signs of pulmonary hypertension and cor pulmonale – loud P2 may not be present due to hyperinflation, tricuspid regurgitation murmur can be heard.

DIFFERENTIAL DIAGNOSIS

1. Bronchial asthma – distinguished by near total post bronchodilator FEV1 reversibility.
2. Bronchiectasis – differentiated by symptoms like hemoptysis, presence of clubbing and radiography.
3. Cystic fibrosis – history since childhood, recurrent infections, presence of other features such as cirrhosis.
4. Broncho pulmonary mycosis
5. Central airway obstruction such as developmental anomalies, tumours, stenosis - differentiated by history and PFT using flow-volume loops.

COMPLICATIONS

1. Recurrent lung/airway infection
2. Bronchogenic carcinoma
3. Cor pulmonale and pulmonary hypertension
4. PTE
5. Pneumothorax especially in those with emphysema
6. Cardiovascular effects – CAD, arrhythmias.

RADIOGRAPHY

XRAY CHEST

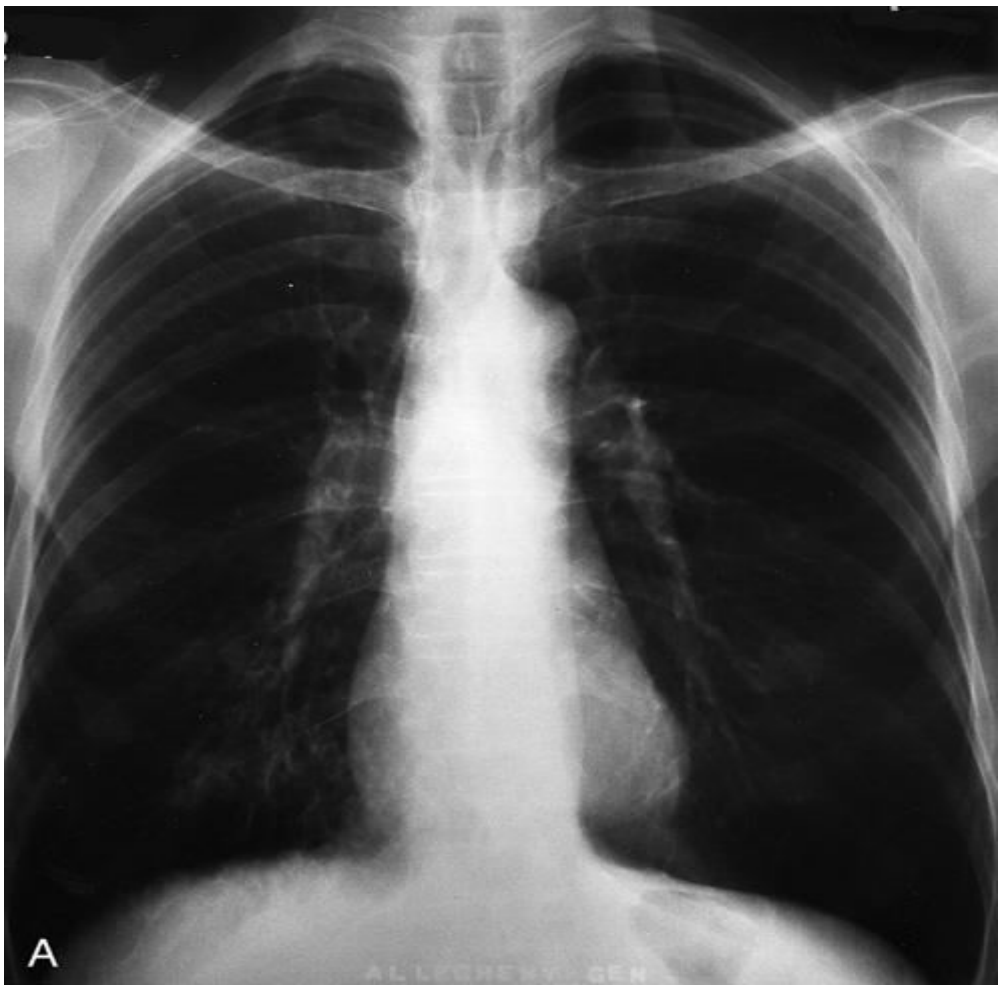
1. CHRONIC BRONCHITIS – increased bronchovascular markings

2. EMPHYSEMA – hyper inflated lung fields

   Diaphragm flattening

   Decreased peripheral vascular markings

   Bulla



3. Pulmonary hypertension – enlarged main and right descending pulmonary artery.
4. To look for co morbidities and complications like malignancy, pneumothorax etc.

COMPUTED TOMOGRAPHY

1. Not routinely done for diagnostic purposes
2. To assess patients fitness for surgical management.

LABORATORY TESTS

PULMONARY FUNCTION TEST:

1. FEV1/FVC < 0.70
2. TLC, FRC, RV may increase often more than normal with disease progression.

Apart from diagnostic utility, FEV1 is also used to monitor treatment response and worsening FEV1 is a poor prognostic factor.

ABG :

1. Normal in early stages.
2. To determine the degree of hypoxemia and the acid base status and to differentiate between acute exacerbations and chronic respiratory failure.
3. Yearly assessment is recommended.

TREATMENT

STABLE PATIENTS

Survival improving strategies

1. Smoking cessation
2. Oxygen
3. Lung volume reduction surgery

Other management strategies are to the relief of symptoms, improving the quality of life and to reduce exacerbations.

DRUGS

BRONCHODILATORS

These drugs are the mainstay of management in that they provide symptom relief and enhance the well-being of patient but do not prevent the decline in FEV1.

INHALED BETA2 AGONISTS :

1. Short acting beta 2 agonist : used in all stages of the disease ‘on demand’ basis to provide immediate relief from dyspnoea and not to be used on a routine basis. Drugs used are salbutamol and levo salbutamol.
2. Long acting : used on a scheduled basis as maintenance therapy to provide sustained relief.

Drugs commonly used are formoterol, salmeterol.

Side effects; tachycardia, tremor, decrease in serum potassium.

INHALED ANTI-CHOLINERGICS:

1. Short acting : for symptom relief similar to short acting beta 2 agonists but are devoid of their sympathetic side effects and also has prolonged action compared to them.

   Drug used is ipratropium.
2. Long acting : for maintenance therapy

   Side effects : dryness of mouth, primary angle closure glaucoma is an absolute contra indication, symptoms of BPH may aggravate.

COMBINATION THERAPY

As the disease worsens, combination therapy with long acting sympathetic and anticholinergic provides maximum symptom benefit by synergistic mechanisms rather than single drug alone.

CORTICOSTEROIDS

INHALED :

ICS are not to be used as a single agent in management of these patients but used in combination with other inhaled bronchodilators.

Indication :

1. Stage 3 disease
2. ≥2 exacerbations / year

Side effects :

1. Oral candidiasis – prevented by mouth gargling after each use or by spacer.
2. Hoarseness of voice.

SYSTEMIC STEROIDS

Oral steroids are not indicated in the regular treatment of stable patients because the adverse effects overweigh the benefits but they are important part of acute exacerbation treatment.

METHYLXANTHINES

Sustained release theophylline is commonly used in patients who do not have adequate symptom relief with inhalational therapy because of its effects on diaphragm function, reducing airway resistance and anti inflammatory action.

Side effects:

These drugs have a narrow therapeutic window and hence supervision is essential.

CVS: increase heart rate, arrhythmia.

CNS: tremor, decreases seizure threshold, insomnia.

GIT: gastritis, nausea.

ANTIBIOTICS – no role in stable patients.

NON PHARMACOLOGICAL MEASURES

OXYGEN

Oxygen therapy improves the morbidity of the patient and reduces the mortality.

Indications

1. Arterial partial pressure of oxygen≤ 55 mm of hg or oxygen saturation by pulse oximetry≤ 88 %
2. Arterial partial pressure of oxygen < 60 mm hg and oxygen saturation < 90% in the presence of pulmonary hypertension, Hct > 55% or cor pulmonale.

VACCINATIONS

For all stages of the disease yearly influenza vaccine and pneumococcal vaccine (zero dose and a booster after 5 years)

PULMONARY REHABILITATION

It is a multi system modality including respiratory exercises, psychological support, adequate nutrition that improves exercise tolerance, improves

breathlessness and quality of life. Indicated in patients failing optimal medical therapy and also for severe disease.

SURGICAL MANAGEMENT

1. LUNG TRANSPLANTATION

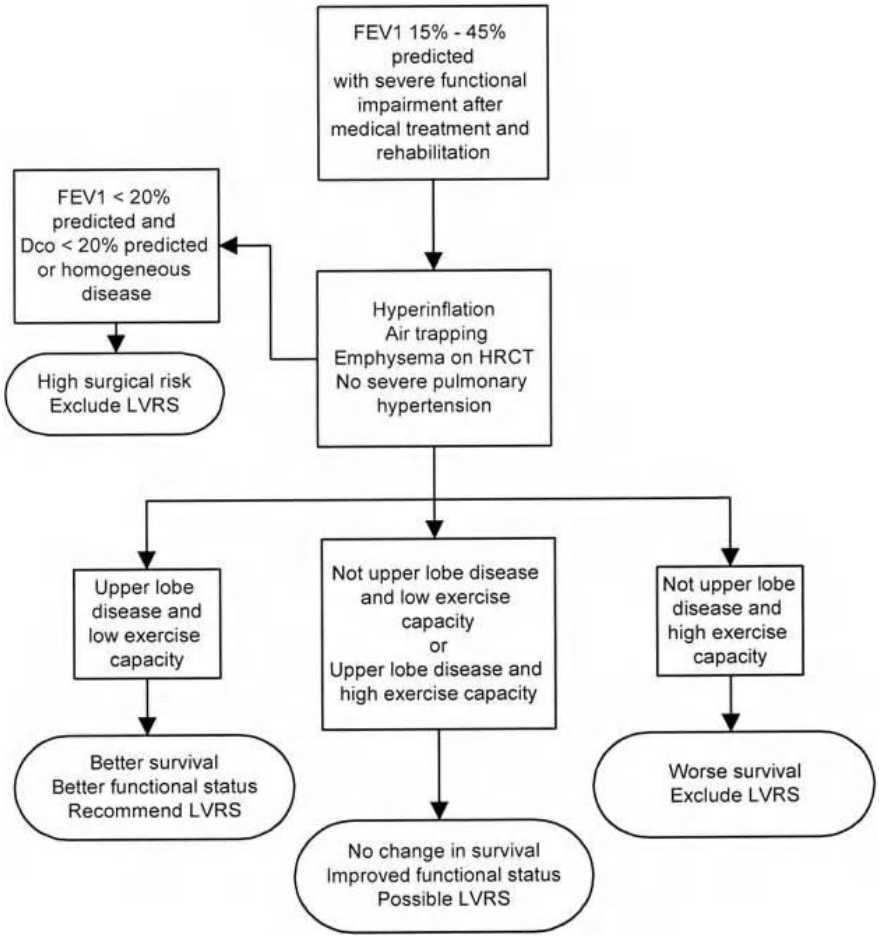
A. Done either as one lung or sequential double lung transplant.

B. Requirements include severe disease inspite of optimal medical management, poor quality of life, absence of other organ system dysfunction.

C. PHT and the region of lung involved are not contraindications.

2. LUNG VOLUME REDUCTION SURGERY

3. Patients with upper lobe emphysema and severely compromised exercise tolerance are model candidates. Presence of PHT/ cor pulmonale are contra indications.



This picture shows that selection of patient for lung volume reduction surgery

4. BULLECTOMY

Stage of COPD	Recommended therapy
All stages	• Active reduction of risk factors, especially smoking • Influenza vaccination • Pneumococcal pneumonia vaccination
I: Mild	• Short-acting bronchodilator when needed
II: Moderate	• Short-acting bronchodilator when needed • Add regular treatment with one or more long-acting bronchodilators when needed • Add rehabilitation
III: Severe	• Short-acting bronchodilator when needed • Add regular treatment with one or more long-acting bronchodilators when needed • Add rehabilitation • Add inhaled steroids if exacerbations are frequent
IV: Very severe	• Short-acting bronchodilator when needed • Add regular treatment with one or more long-acting bronchodilators when needed • Add rehabilitation • Add long-term oxygen therapy if chronic respiratory failure is present • Consider surgery • Add inhaled steroids if exacerbations are frequent

Source: Adapted from Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease.[15]

This above points suggest stages wise approach to patient with COPD.

EXACERBATION OF COPD

PRECIPITATIING CAUSES

Infections

1. Bacterial infections
    a. Pneumococcus
    b. Haemophilus influenza
    c. Moraxella catarrhalis
    d. Pseudomonas in special risk groups.
2. Viral infections

Environmental

1. Pollution
2. Exposure to toxic gases
3. Climate changes

SYMPTOMS

1. Increase in cough
2. Worsening dyspnoea
3. Increased sputum with purulence
4. Worsening general condition

To assess the severity of exacerbation complete physical examination is mandatory.

Investigations include

1. X ray chest – to detect pneumothorax, consolidation
2. ECG – to detect rhythm disturbance, most common being MAT
3. ABG – to detect respiratory failure.

Based on the severity patient general status, supportive care, presence of other co morbidities like CAD, diabetes, ABG measurement and the need for assist ventilation, the decision is taken whether the patient has to be treated at home or hospital or ICU.

Detecting the COPD mortality in exacerbation of COPD, BODE index is very useful.

BODE INDEX

Variable	**0**	**1**	**2**	**3**
FEV_1 (% of predicted)	≥65	50-64	36-49	≤35
Distance walked in 6 min (meters)	≥350	250-349	150-249	≤149
MMRC dyspnea scale	0-1	2	3	4
Body mass index	>21	≤21		

DRUGS

BRONCHODILATORS

Short acting beta agonists are used in primary treatment for exacerbation of COPD, either alone or in addition with an anticholinergic delivered through nebulisation or inhalation if patient can perform. Those patients who are already on methyl xanthine, it should not be stopped as it causes deterioration but monitoring of drug level is mandatory. During an exacerbation theophylline should not be prescribed.

CORTICOSTEROIDS

For short course systemic corticosteroids either oral or parenteral is a important cornerstone in management of acute exacerbation because the decrease hospital

stay improves lung function decreases the subsequent hospital admissions due to exacerbation.

ORAL CORTICOSTEROIDS

Prednisolone at a dose of 30 to 40 mg or its equivalent has to be given for 10 to 14 days.

The proven advantages are early recovery, lung function improvement, improvement in arterial hypoxemia, decrease in length of hospital stay.

INHALED CORTICOSTEROIDS

Nebulised budesonide can be used as an alternative for oral corticosteroids.

ANTIBIOTICS

Pro calcitonin III – specific for bacterial infection could be used to guide antibiotic therapy.

INDICATIONS FOR ANTIBIOTICS IN ACUTE EXACERBATION

1. Increase in dyspnea
2. Increase in sputum volume
3. Purulent sputum
4. Patient requiring mechanical ventilation.

   Duration 5 to 10 days.

OXYGEN THERAPY

Spo2 should be maintained ≥ 90%. Oxygen must be given and should not be with held for fear of respiratory depression due to removal of hypercarbic stimulus because it is very important to prevent tissue hypoxemia but care should be exercised in monitoring the patient.

After 6 minutes of oxygen therapy ABG should be performed to ensure adequate oxygenation without acidosis.

Ventury masks are preferred because of it's controlled delivery and its accuracy.

NON INVASIVE POSITIVE PRESSURE VENTILATION

Currently it is preferred for patients with COPD requiring mechanical ventilator support for reason like

1. Discomfort to the patient is very less.
2. Less risk of infections.
3. It counter balances the disadvantage of PSV and CPAP when used alone.

INDICATIONS FOR NIPPV INCLUDES

1. Severe dyspnoea with respiratory muscle fatigue
2. Respiratory acidosis

To consider a patient for NIPPV any one of the above is essential.

INDICATION FOR INVASIVE MECHANICAL VENTILATION

1. Nov-invasive positive pressure ventilation failure
2. Severe bradycardia
3. Cardiac and or respiratory arrest
4. Severe tachypnea
5. Uncontrolled respiratory secretions
6. Hemodynamic instability
7. Aspiration
8. Altered consciousness

SYSTEMIC MANIFESTATION OF COPD

It has been identified from the experiences in the past decades that inflammation is no longer confined to lungs in COPD and that GOLD definition of the disease at present includes 'some significant extra pulmonary effects that may contribute to the severity in individual patients'. Therefore the disease could be renamed as chronic systemic inflammatory syndrome.

MARKERS OF SYSTEMIC INFLAMMATION IN COPD

1. white blood cell count
2. ferritin
3. fibrinogen

4. hsCRP
5. TNF alpha receptor polymorphism
6. TGF beta 1
7. Interleukins
8. ROS

These markers are present in mild markers of disease and their levels increase with increasing disease severity.

HYPOTHESIS

1. Probable inflammation spreading over to CVS, CNS etc.
2. A pro inflammatory phenotype is happening independent of lung component in systemic inflammation.

TRIGGERS

1. Smoking an important risk factor for the disease per se by way of endothelial function dearangement and oxidative stress to the tissues.
2. Hypoxia of severe disease enhances HIF – 1 expression, upregulates genes invlolved in new vessel formation, inflammation, vascular remodelling. TNF alpha levels have been shown to be in correlation with hypoxemia severity and that the enhanced survival of patients on LTOT might be due to fact that oxygen decreases inflammation.
3. Increased leptin levels and its receptors

4. Autoimmune process
5. Oxidative stress of the disease shorten the telomere and causing ageing of lungs and other systems.

CONSEQUENCES

The consequence of the systemic inflammatory process are non pulmonary morbidities and mortalities shown to have immediate cause effect relationship across studies consistently and also have been identified that their association is not just by chance.

CARDIOVASCULAR SYSTEM

1. CORONARY ARTERY DISEASE

These patients have three fold increased risk of developing CAD and the mortality rates in these patients due to CAD are correlate to those due to worsening of disease per se. cardiac injury biomarkers are increased in studies during acute exacerbations when the level of systemic inflammation is high.

2. ARRHYTHMIAS

The common rhythm disturbance include

a. multifocal atrial tachycardia
b. ventricular tachycardia
c. atrial fibrillation

3. **CARDIAC FAILURE**

   Cardiac failure is precipitated by end diastolic pressure changes induced by pressure variation caused by hyperinflation which interferes with ventricular remodelling.

SKELETAL MUSCLE WASTING

1. More common in patients with severe COPD
2. Proposed mechanisms include reduced IGF-1, decreased IL-6, decreased testosterone, decreased intake, hypoxemia.
3. Fat mass will be relatively preserved when compared to skeletal muscle mass.
4. It will have ill impact on exercise capacity and respiratory function.

   It is one of the negative predictor for outcome in COPD patients.

   OSTEOPOROSIS

   1. Seen in COPD patients who have never been on steroids
   2. It is related to tumour necrosis factor alpha and IL-1.
   3. It helps the macrophages to convert to osteoclasts.
   4. Other factors that may worsen the problem are increasing age, smoking, malnutrition, poor physical activity.

   METABOLIC SYNDROME AND DIABETES MELLITUS

Undoubtedly, increased prevalence of diabetes in COPD patients are seen due to systemic inflammation which is strengthened by finding of elevated levels of inflammatory markers such as TNF alpha, IL-6 and CRP which further compounds the risk for developing CVD.

DEPRESSION

Increased prevalence due to

1. systemic inflammation
2. dependence due to increased disability
3. impaired quality of life.

PULMONARY HYPERTENSION IN COPD

Mild PHT to some extent occur in most of the patients with advanced disease and rarely severe pulmonary hypertension in few.

CAUSES

1. Pulmonary vasoconstriction due to alveolar hypoxia acidosis, hypercapnia.
2. There is decrease in small vessels in areas of destroyed lung tissue due to terminal air space destruction seen in patients with emphysema.
3. Increased lung volume leading to compression of pulmonary vessels.

4. For every acute exacerbation there is approximately 20 mm of hg rise in pulmonary arterial pressure. This ultimately end up in pulmonary hypertension in repeated exacerbation.

MECHANISM OF PULMONARY HYPERTENSION BY HYPOXIA

1. Vascular intimal thickening
2. Distal vessels vascularisation
3. Hypertrophy of the vascular media of the proximal vessels.

TREATMENT

Pulmonary vasodilators result in worsening of V/Q mismatch because it is not the level of pulmonary hypertension but the degree of hypoxia which produce the clinical symptoms and that these drugs further worsen the situation.

The only proven treatment is oxygen therapy which decreases both morbidity and mortality.

To keep the haemoglobin in upper limit of normal because low haemoglobin is not tolerated in these patients due to hypoxemia.

Nocturnal or ambulatory SaO2 can assist in optimal O2 concentration.

COR PULMONALE

it can happen either acutely during exacerbations or chronically due to disease progression and worsening gas exchange and produces irreversible vascular remodelling.

DIAGNOSIS

1. Echocardiogram

   To identify the presence of right ventricular enlargement but the study is difficult due to hyperinflated lungs and rotation of the heart. It can be supplemented by ABG-showing PaO2 < 50 mm Hg and Pco2 >50 mm hg.
2. Electrocardiogram
3. Cardiac catheterization – the gold standard investigation.

   MANAGEMENT

   1. Acute cor pulmonale
      a. Treatment of the precipitating cause
      b. Supplemental o2 to maintain adequate oxygenation.
   2. Chronic cor pulmonale

      Should be very careful while using diuretics and digoxin in patients with cor pulmonale because it sensitizes the heart to digoxin and precipitates life threatening rhythm disturbances in the presence of hypoxia and acidosis.
   3. Oxygen

SPIROMETRY IN COPD

The test to confirm or refute a diagnosis of the disease is spirometric evaluation as suggested by GOLD. As of them a post bronchodilator Forced expiratory volume 1/ Forced vital capacity < 70% is used for diagnosis and the previous concept of absence of post bronchodilator reversibility has been abandoned. Spirometry has its own limitations and therefore a combination of clinical symptomatology and spirometry improves the diagnostic accuracy.

ELECTOCARDIOGRAM IN COPD

Chronic obstructive airways disease influence the electrical events of the heart in the following basic respects:

1. the voluminous lungs have an insulating effect and thereby diminish the transmission of electrical potential to the registering electrodes
2. the heart descends to a lower position within the thorax due to a lowering of the diaphragm. This will alter the position of the heart relative to conventional precordial electrode postions.
3. the right ventricle and right atrium become compromised due to a reduction of the pulmonary vascular bed. This will result in right ventricular hypertrophy as well as right atrial enlargement.this right atrial enlargement lead to change in P wave vertical axis.

Decreased magnitude of the electrocardiographic deflexions

The voluminous lungs impair electrical transmission. The QRS and T deflexions are therefore markedly diminished in magnitude.

Lead I sign

In patients with COPD the frontal plane P, QRS and T wave axes are not infrequently all directed at around + 90 degree which are either precisely or almost perpendicular to the standard lead I axis. As a result of this Lead I reflects absent or very low amplitude P, QRS and T wave complexes giving the appearance of minimally disturbed base line. This ECG phenomenon is known as the Lead I sign.

Right atrial enlargement

Depolarization of atrium represented by the P wave. Normal frontal plane P wave axis is directed to the right of +60 degree. In lead I and lead II and left precordial leads, the P wave is upright. Lead III biphasic P wave may be seen .Initial positive portion of the P wave indicate, activity of right atrium. Terminal negative portion indicate, activity of left atrium.

The cause for P-axis verticalisation in lung hyperinflation is that the right atrium is sturdy attached to the diaphragm by means of dense pericardial ligament around the inferior vena cava. Due to progressive flattening of the diaphragm, the right atrium is distorted/displaced inferiorly causing a significant rightward deviation (verticalisation) of the P-wave axis.

In contrast, in pure restrictive (fibrotic) lung disease, correlating with the degree of diaphragmatic elevation, the P-wave axis tends to be horizontal or leftward.

The vertical P wave axis degree inversely correlating with FEV1, directly proportional to disease severity

P pulmonale

It is reflected by P waves which are tall and peaked in standard leads II, III, aVF, and is the expression of right atrial enlargement.

The combination of right axis deviation and tall peaked P waves is Called P pulmonale. A comparison of interstitial pulmonary fibrosis and COPD showed that a deviation of the frontal plane P wave axis to the right of +70 degree only occurs with COPD.

Abnormalities of the QRS complex

Right QRS axis deviation

The frontal plane QRS axis is deviated to the right and commonly directed to +90 degree. When it is deviated further, the frontal plane leads will usually reflect an S1Q3R3 pattern. In very severe cases it may be directed to the “northwest” region.

Left QRS axis deviation

This occurs in about 10% of cases. The mechanism is still speculative.

S1, SII, SIII syndrome

Prominent terminal S waves may appear in standard leads I and II or in

I, II and III giving rise to the SI, S II, S III syndrome. This indirectly reflects posterior displacement of the apex.

Posterior displacement of the mean QRS axis

The mean QRS axis may also be displaced somewhat posteriorly so that it tends to be more obliquely oriented to the horizontal plane.

13

Abnormalities of the precordial QRS form

There is diminution of QRS magnitude in all the leads. It is not uncommon for all the precordial leads to reflect rS complexes. In very severe cases the R : S ratio is usually less than 1 in leads V4 to V6, and R wave amplitude in lead V6 may be less than 5 mm. The transition zone is frequently displaced to V6 or even further to the left.

Right bundle branch block

There may occasionally be transient complete or incomplete RBBB with an exacerbation of the emphysema and increase in oxygen desaturation.

Right ventricle hypertrophy is mainly reflected by:

a. right axis deviation

b. prominent terminal S waves in the left precordial leads

The single most characteristic ECG feature of diagnosis in COPD is said to be P wave axis of +70 to +90 degrees.

Abnormalities of T waves

Frontal T wave axis

It is usually similar in direction to that of QRS axis. The T wave is diminished in amplitude in all leads. The T wave may be inverted in the right precordial leads especially when pulmonary hypertension is marked. Exacerbation of the disease with an increase in oxygen desaturation may be associated with elevation of ST segment in leads II, III and AVF. This manifestation is reversible.

USES

1. Diagnosis
2. Grading of severity In COPD patients the rate of decrease in forced expiratory volume 1 per year is about 75-100 ml in sharp contrast to normal persons' 30 ml/ year.
3. Lung "age" assessment

   By correlating patient's FEV1 to the predicted FEV1 of his age matched control. It may be used to encourage smokers to quit smoking.
4. Detection of upper airway obstruction

5. Pre-operative evaluation

   These patients have a higher chance of developing post-operative pulmonary complications.

   1. Thoracic surgery

      Predicted post operative FEV1 is calculated by applying "rule of 5" in that $1/5^{th}$ function is contributed by each lobe and the predictive post operative value is calculated by lobe to be removed. A PPO FEV1 < 40% predicted is a contra indication to surgery.

   2. Non thoracic surgery

      Factors predicting post-operative complications are

      a. FEV1/FVC < 50%
      b. Maximum voluntary ventilation< 50%
      c. FEV1 or diffusing capacity <20% predicted
      d. High partial pressure of Co2
      e. Short distance of surgical site from the chest

SMOKING CESSATION

Smoking cessation is most important intervention in stopping the disease process.

APPROACH

A. Counselling

B. Pharmacological assistance.

COUNSELLING

Counselling either by the clinician or non clinician increases cessation rate many times than self initiated attempts.

5A intervention approach

1. ASK – information about tobacco use at every visit.
2. ADVICE – should be strong and individualized depending on patient's health status and other considerations.
3. ASSESS – patient's willingness. If patient is not willing he should be insisted to quit.
4. ASSIST – by speaking with the patient a give up plan; setting a date to stop smoking in the next 2 weeks, to reduce alcohol use, educate households and providing psycho social support.
5. ARRANGE – follow-up.

PHARMACOTHERAPY

First line agents

Nicotine replacement therapy

Formulations available

Gum

Dose : 2 mg – 1-24 cigarettes/d; 4mg ->25 cigarettes/d

Duration : 12 weeks

Adverse effects : dyspepsia

Lozenge

Dose : 2mg – first smoke > 30 min after waking up from bed; 4mg – first smoke < 30 min after waking up from bed.

Maximum of 20 mg/d

Duration : 12 weeks

Side effects : nausea, insomnia.

Inhaler

Dose : 6-16 cartridges of 4 mg each/d

Duration : 6 months with dose reduction in last 3 months

Side effects : rhinitis, local irritation

Spray

Dose : 0.5 mg in Each nostril 1-2 doses/he

Maximum 5/he

Duration : 3-6 months

Side effects : local irritation

Patch

Dose: 16 or 24 hr patch for total duration of 8 weeks with dose reduction

Side effects : local skin reaction, insomnia

Advantage : good compliance, requires less skill.

Contra indication to NRT :

1. CAD – MI or unstable angina
2. CVA
3. Untreated acid peptic disease

Bupropion sustained release

Mechanism of action

nor-epinephrine and dopamine reuptake inhibitor

dose : 150 mg once daily x 3 days; 150 mg bd x 7-12 weeks

duration: 6 to 12 months

side effects : insomnia, dry mouth

contra indications : epilepsy, MAOI use in past 2 weeks

particularly preferred in patients with concomitant depression

varnecline

mechanism of action

partial agonist of nicotinic ach receptor

dose : 0.5 mg od x 1- 3 days; 0.5 mg bd x 4-7 days; 1mg bd from then up to 8 weeks.

Side effects : CNS – suicidal intention which has resulted in FDA warning.

Second line agents

1. Clonidine :

   Mechanism of action : post synaptic alpha2 agonist

   Dose : 0.1 – 0.4 mg/d x 2-6 weeks
2. Anxiolytics

   Diazepam, buspirone, beta blockers
3. Sensory replacement

   Citric acid inhaler, denicotinised tobacco, black pepper extract.
4. Acupuncture : by releasing endorphins

ANTAGONISTS

Mecamylamine

Non competitive CNS and PNS nicotine receptor antagonist

1. Naltrexone

   Aversion causing drugs

   Silver acetate – poor compliance

SMOKING PREVENTION

Smoking behaviour in around 90% smokers were initiated during adolescence. So prevention is more important and effective than cessation after the behaviour has begun.

Measures :

1. Health education – target population : adolescents, young adults
2. Public health programs
3. Smoke free public places.

EMERGING THERAPIES

The imbalance between pulmonary oxidant load and anti-oxidants leads to oxidative stress and causes inflammation and airway modelling. This functions as an important pathogenetic mechanism and probably the reason for steroid resistance and so has been targeted for newer therapies.

So newer drugs are developed with the aim to inhibit this one of the several steps involved in the inflammatory pathogenesis of COPD with the concern of developing effective but also safe drugs.

SMOKING CESSATION

Smoking cessation is considered to be an important and effective intervention to halt the decline of lung function beyond any doubts. And now recent research has developed anti-free nicotine antibodies.

These anti free nicotine antibodies bind with free nicotine denying their access across the blood brain barrier. And hence nicotine from cigarettes cannot stimulate nicotine receptors causing smoking an unpleasant experience

NEWER BRONCHODILATORS

Bronchodilators provide immediate symptom relief even though they do not arrest the disease process and thereby improve wellbeing of the patient. Hence this serves as an important component of the treatment plan.

So for this purpose, newer long and ultra long acting bronchodialtors have been developed with the aim of meeting the short comings of short acting ones which is poor compliance due to multiple dosing. These ultra long acting bronchodilators are ultra long acting muscarinic antagonists and ultra long acting beta2 agonists.

ULTRA LONG ACTING MUSCARINIC ANTAGONISTS

These agents have been shown to decrease the number of exacerbations besides providing long acting bronchodilatation and

so they have the ability to attenuate the disease process partially and hence provide mortality benefit.

DRUGS UNDER RESEARCH :

1. Dexpironium
2. Daratropium bromide
3. Aclidinium
4. TD-4208
5. GSK-573719
6. Glycopyronium bromide

ULTRA-LONG ACTING BETA2 AGONISTS

This includes

1. Vilanterol – safe and efficacious
2. Indacaterol – approved in Europe and USA
3. Carmoterol – using modulate technology, the amount of inhaled drug reaching the target has been increased.
4. GSK-642444
5. MILVETEROL – PROVED EFFICACIOUS IN ASTHMA, NOT YET RESEARCHED ON copd
6. BI-1744-CL
7. UK-503590
8. Compound X

NOVEL COMBINATIONS

Rationale of combining long acting drugs

1. Synergism between two agents
2. Patients are analysed whether beta or muscarinic receptor predominance in their airway respond to their respective drugs more than the other. So that their combination can overcome the problem of receptor variation.

Though several combination of these agents along with steroids to decrease exacerbations are under development, there is a potential limitation of using these combination. The limitation is that delivery of these agents at different site which decrease their synergism. But still a solution which could overcome these limitation has been witnessed. It is by combining them into a dimer which serves to deliver the agents at the same site – dual acting muscarinic antagonist beta 2 agonist.

Even other combinations under development are combining a LABA with an ICS or combining LABA with inhaled steroid and LAMA.

ANTI INFLAMMATORY DRUG

Over the decades there has been search for an effective and safe anti inflammatory drug with the potential of reducing lung inflammation. But still it has turned out to be in vain.

But one of the recent break through finding is that oxidative stress causing decrease in HDAC in these patients has been the reason for corticosteroid unresponsiveness in them. And that theophylline increases this enzyme at cellular levels. Hence theophylline has made a comeback in the management of the disease with the aim of additive anti inflammatory effect when given with steroids and studies are underway.

PDE-4 INHIBITORS

Phosphodiesterase-4 is an enzyme found specifically in most inflammatory cells. This has been targeted to reduce the inflammatory process of the disease. So a selective PDE-4 inhibitor has been approved for use. This has shown to increase FEV1 comparatively much better than tiotropium. And hence these drugs could be the best adjuvant therapy with bronchodilators. It is under study to introduce an inhalational form of this class. The key problem is that the side effects of this drug – gastro intestinal and upper respiratory tract effects. And this has led to search for development for specific inhibitors.

ANTIPROTEASES

As discussed earlier. An important pathogenetic mechanism of emphysema is an imbalance between proteases and anti proteases. Anti proteases such as MMP inhibitors have shown promising results in preventing emphysema. But few drugs of this class are under phase II and phase III trials.

1. AZ11557272 – dual MMP-9/MMP-12 inhibitor
2. Marimastat – non selective MMP inhibitor

CYTOKINE INHIBITORS

Obviously TNF alpha and other interleukins – notably IL-6, IL-7, IL-1beta are important cytokines responsible for the systemic inflammatory process in the disease. But still drugs targeting these cytokines are only in the budding stage.

CHEMOKINE ANTAGONISTS

CXCR1/2 receptor mediates the effects of chemokines on inflammatory cells. Oral AD28309, which is the antagonist to these receptor has shown to reduce inflammation in man. CXCR 3 and 5 are other receptors targeted and drugs involved in these have finished phase I trials.

TGF BETA INHIBITORS

TGF beta causes small airway fibrosis and hence results in decrease in FEV1 and reduced exercise capacity. SD-280 is a class which inhibits this fibrogenic cytokine has been developed for this purpose but the long term consequences of this class are yet unknown.

NFKB INHIBITORS

NFKB is a transcription factor involved in upregulating the production of various chemokines, TNF ALPHA and MMP-9. And hence inhibition of this transcription factor seems to be a potential option. But such inhibitors are presently under research.

P38MAPKinase INHIBITORS:

P38MAPKinase is an enzyme which upregulates the production of interleukin 8, TNF ALPHA and few other mediators causing inflammation. Inhaled formulation of inhibitors of this enzyme are now in development period.

PHOSPHOINOSITOL-3-KINASE INHIBITORS under research.

PPAR AGONISTS

The drugs currents being studied for immunomodulatory effects of PPAR alpha and gamma are rosiglitazone and SB-219994.

ANTIOXIDANTS

Anti oxidant drugs being used are

1. NAC and its derivatives

a. N-Acetyl Cysteine

i. Decreases systemic and pulmonary oxidative stress

ii. Mild bronchodilation

iii. Reduces exacerbation

iv. Halts decrease in FEV1

b. N-acestelyn – well tolerated

c. Erdosteine – added advantage of reducing bacterial adhesion thereby reducing exacerbations.

d. Procysteine – toxic

e. Carbocysteine

f. N – isobutyryl cysteine – less effective

2. NRF-2 activators

STATINS

There are plenty of pleomorphic action of statins apart from lipid lowering action such as

1. Anti oxidant
2. Endothelial protection and

3. Anti inflammatory properties
4. Reduce exacerbations
5. Decrease need for assisted ventilation
6. Improving functional capacity
7. Reduce FEV1 decline

But randomised controlled trials are required to confirm their effectiveness to be included in the management plan of COPD.

REGENERATIVE THERAPIES

There are plenty of modalities to decrease or bring the destroyed lung back and hence restoring the normal anatomy. But currently only research is focusing on these modalities which in future if discovered might revolutionize the COPD management.

STEM CELLS

Restoration of alveolar tissue can be achieved by allogeneic mesenchyme stem cells but this modality has a main disadvantage. i.e. it may lead to an undesirable outcome of clogging of pulmonary vasculature with these cells. But still trials are currently under research to overcome this undesirable side effect.

RETINOIC ACID

Regeneration of distal respiratory unit can be achieved by ATRA and it also reverses emphysema but these benefits had not been shown in clinical trials.

ANTI-AGEING THERAPY

Accelerated ageing is found to be caused by oxidative stress which increases DNA damage mediated by inactivation by SIRT1 or SIR2 protein1. And this is being focused as a target for arresting the disease process.

These discoveries are going in progress on one side. On the other side research are also on to find a better way of enhancing the amount of drugs delivered to the desired segment of lung by using either new carrier formulation, liposomal formulations, nanotechnology or agents to enhance absorption such as surfactant, taurocholate, hyaluronic acid etc.

The best and most effective intervention is cessation of smoking though several hundreds or thousands of newer treatment modalities/drugs may emerge.

MATERIALS AND METHODS :

STUDY POPULATION:

The study is to be conducted on 100 patients of Government Rajaji Hospital, who are all attending internal medicine and thoracic medicine op with clinical features and ECG changes of COPD

INCLUSION CRITERIA:

1. Age >45 year
2. Normal sinus rhythm with ECG change
3. past medical history of COPD
4. Imaging studies with COPD changes
5. Pulmonary function tests with COPD changes

EXCLUSION CRITERIA

1. Congenital heart disease
2. valvular heart disease
3. Cardiomyopathy.

Most of the patients were diagnosed clinically and after radiological investigation.

ANTICIPATED OUTCOME:

Vertical axis of P wave inversely correlating with pulmonary function test in COPD

DATA COLLECTION:

All the patients selected for study are confirmed cases of COPD.

LABORATORY INVESTIGATIONS:

1) **X ray chest**
2) **ECG**
3) **Pulmonary function test**

STUDY PROTOCOL

DESIGN OF STUDY:

Observational study

PERIOD OF STUDY:

July 2014 to October 2014

ANALYSIS:

Statistical analysis

PARTICIPANTS:

Patients attending in medicine and thoracic medicine op with clinical features and ECG changes of COPD

CONFLICT OF INTEREST:

NIL

FINANCIAL SUPPORT:

NIL

OBSERVTION AND RESULTS

A total of 100 cases were studied. Data collected from patients were entered in Microsoft excel 2010 spread sheet and analysed with simple statistical analysis

Table 1 Distribution of patients in each stage

S.No	Stage	No. of patients	percentage
1.	I	20	20 %
2.	II	15	15 %
3.	III	31	31 %
4.	IV	34	34 %
Total		100	100 %

of the 100 patients ,20 patients (20%) were in stage I, 15 patients (15%) were in stage II, 31 patients (31%) were in stage III, 34 patients (34%) were in stage IV.

Chart 1 Distribution of patients in each stage

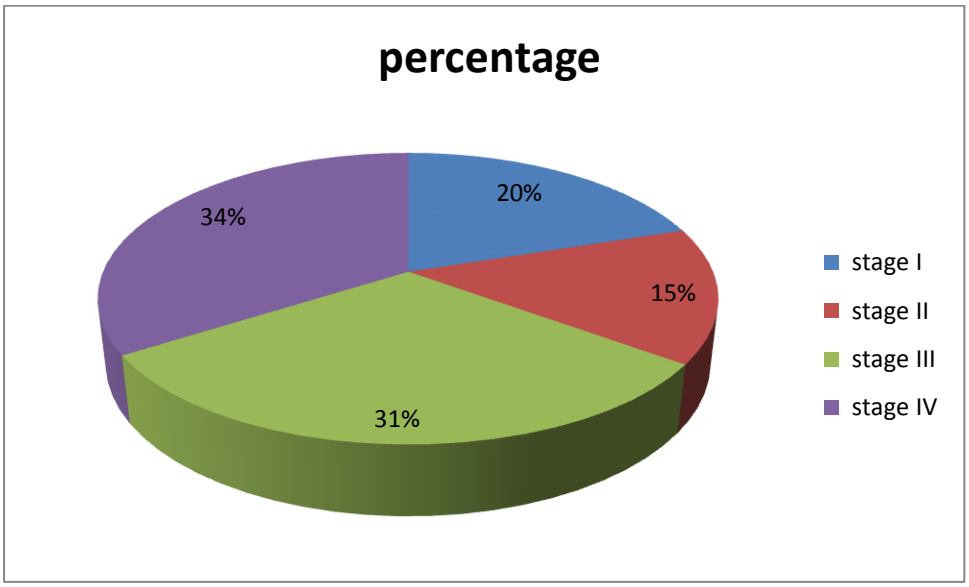


Table 2 Age distribution of patients in each stage

Age distribution	Stage I	Stage II	Stage III	Stage IV	Total
40 – 50	6	4	10	0	20
51 – 60	7	6	8	12	33
61 – 70	7	5	6	7	25
71 – 80	0	0	7	15	22
Total	20	15	31	34	100

the maximum number of patients belonged to the 51-60 age group and 40 -50 age group constitute the minimum

Chart 2 Age distribution of patients in each stage

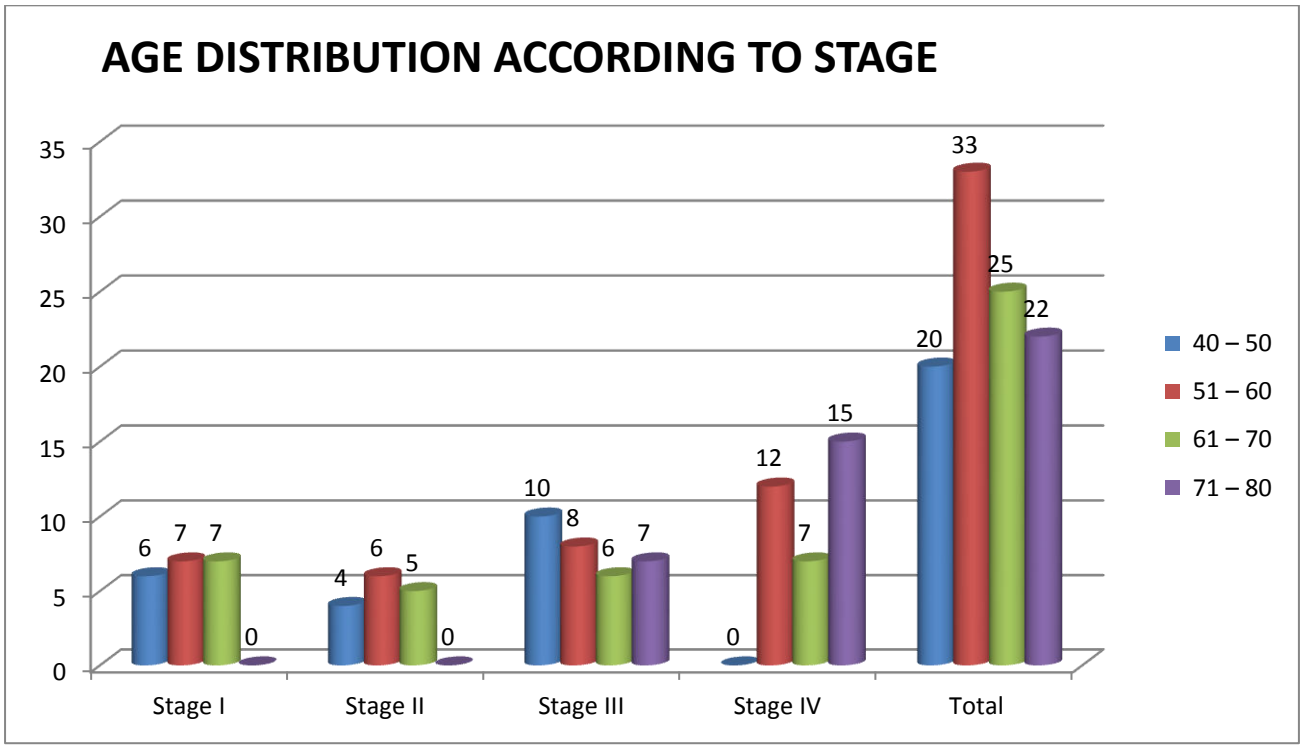


Table 3 Mean age distribution in each stage

S.no	stage	Mean age ± SD
1.	I	57.95 ± 7.39
2.	II	56.73 ± 8.08
3.	III	60.09 ± 10.74
4.	IV	66.52 ± 8.54
p <0.001 significant		

AGE WITH FEV1 % OF PREDICTED VALUE

FEV1 PV	P VALUE
AGE	0.004

The increasing in age with the increasing stage of the disease was found statistically significant with p <0.001 and the correlation of age with FEV1 % of predicted value was found to be statistically significant

Chart 3 Mean age distribution in each stage

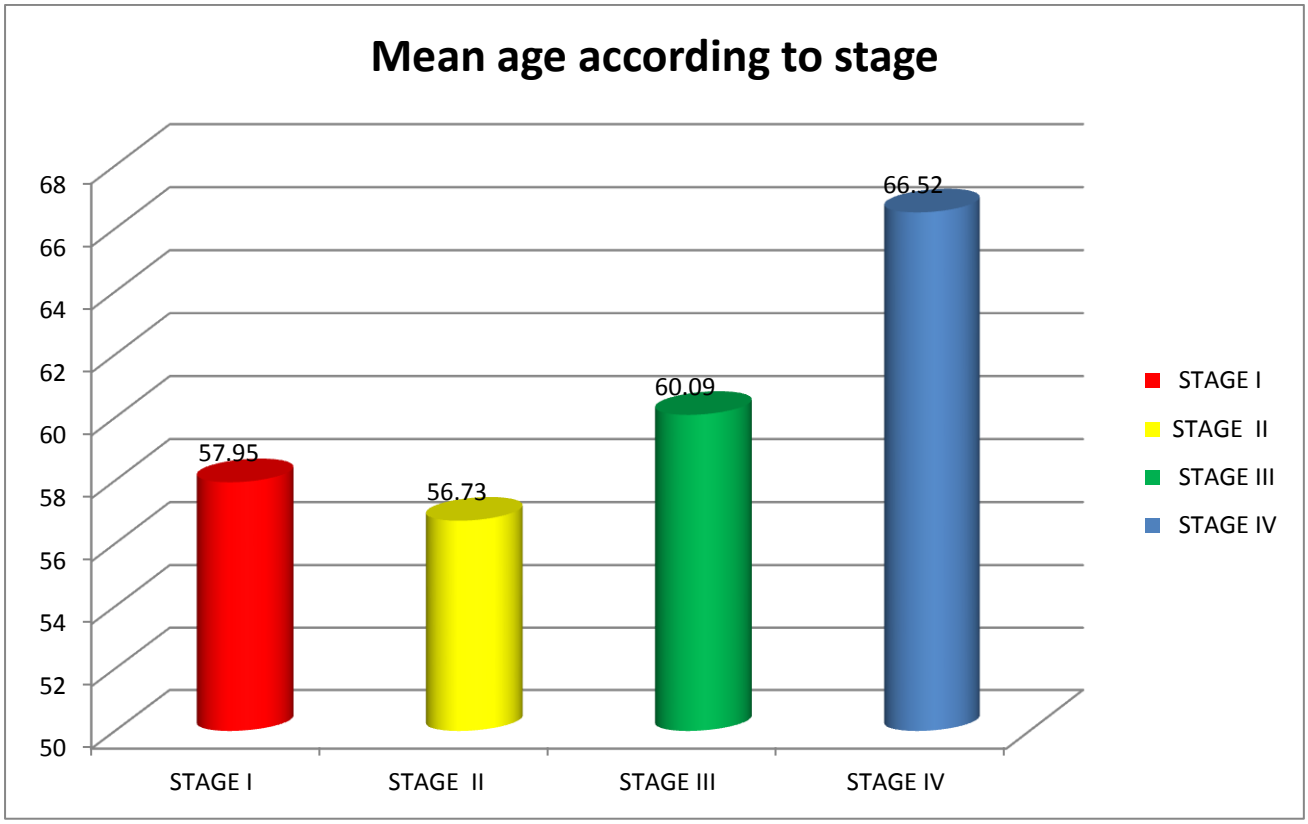


Table 4 No of patients according to smoking habits

Smoking Habits	No of patients	% of patients
Smokers	67	67 %
Non smokers	33	33 %

Of the 100 patients 67 patients belongs to smoker and 33 patients are non-smokers

Chart 4 No of patients according to smoking habits

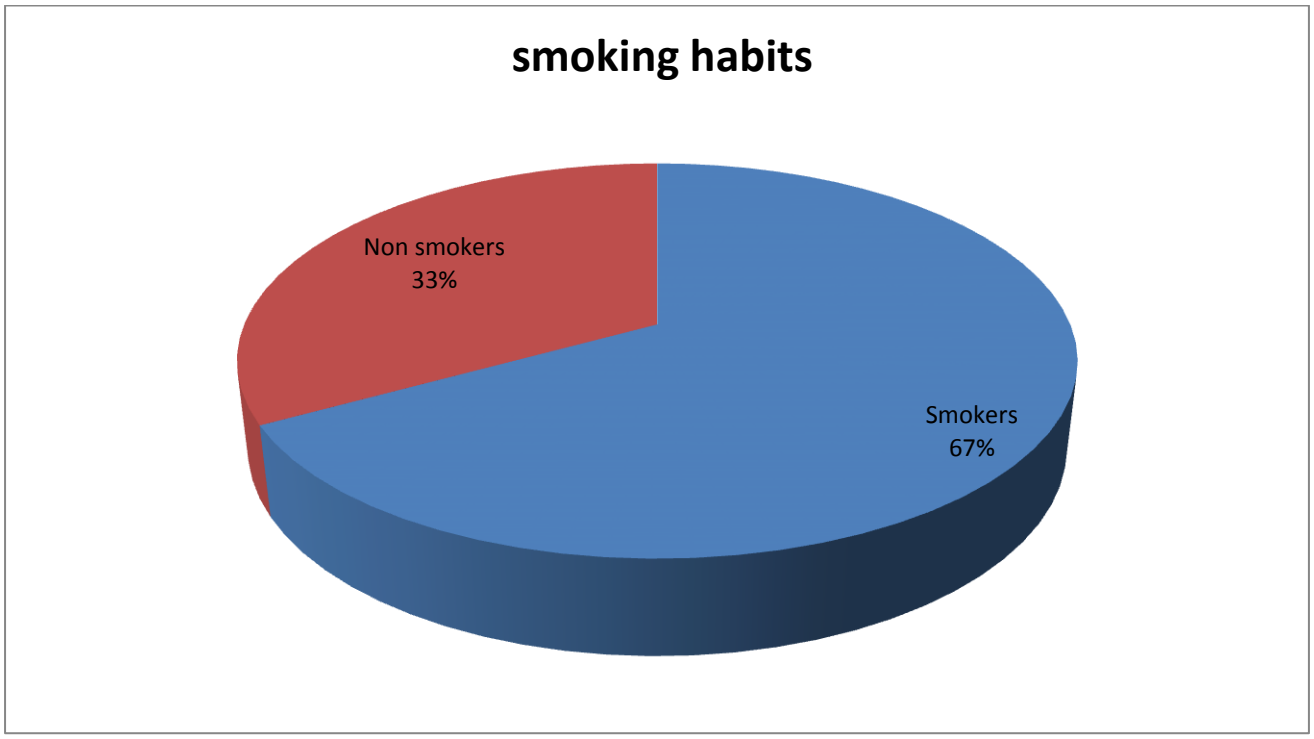


Table 5 Sex distribution according to stage

Stage	Male		Female	
	No. of patients	**%**	**No. of patients**	**%**
I	**16**	**21.9**	**4**	**14.8**
II	**9**	**12.3**	**6**	**22.3**
III	**24**	**32.9**	**7**	**25.9**
IV	**24**	**32.9**	**10**	**37**
Total	**73**	**100**	**27**	**100**

of the total 100 patients 73 patients were male and 27 patients were females .

Chart 5 Sex distributions according to stage

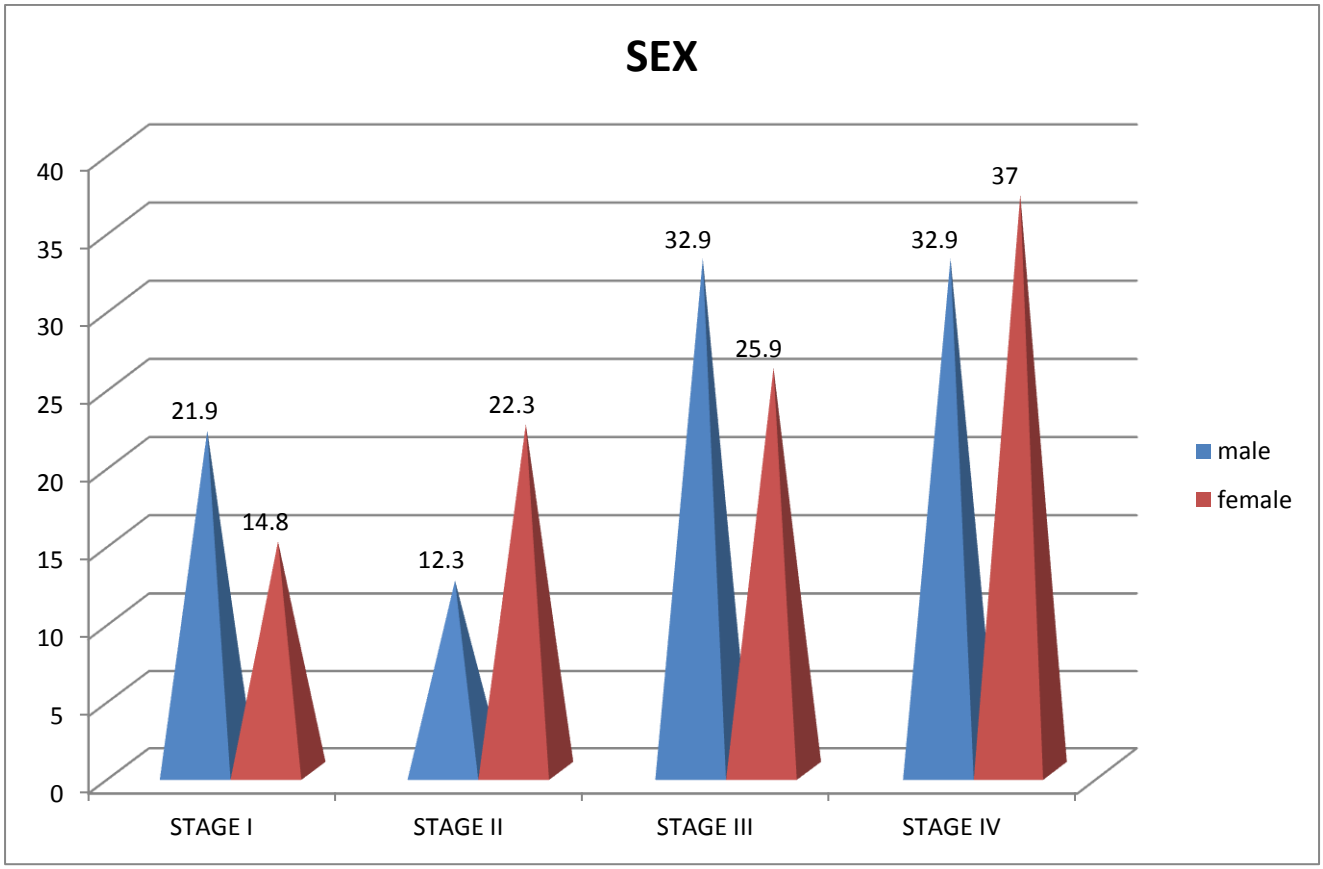


TABLE 6 OCCUPATIONS

S.NO	OCCUPATION	No of patients	Percentage (%)
1	Manual labourers	60	60
2	Dye industry	9	9
3	Professional	10	10
4	Flour mill	10	10
5	Business	4	4
6	Cotton industry	7	7
Total		100	100

Of the total of 100, Manual labourers were 60, Dye industry workers were 9, Professional were 10, Flour mill workers were 10, Business were 4, Cotton industry workers were 7.

Table 7 symptoms

S.NO	Symptoms	No. of patients
1	Chronic cough	100
2	Sputum production	70
3	Breathing difficulty	90
4	Wheeze	80

All the patients had chronic cough, 70 patients with sputum production, 90 patients with Breathing difficulty, 80 patients with Wheeze.

Table 8 SIGNS

S.NO	signs	No. of patients
1	Elevated JVP	35
2	Pedal edema	27
3	Diminished air entry	75
4	Rhonchi	90
5	Crackles	52
6	Downward displacement of liver	42

Of the 100 patients, 35 had Elevated JVP,27 patients had Pedal edema , 75 patients had Diminished air entry, 90 patients had Rhonchi, 52 patients had Crackle and 42patents had downward displacement of liver

Table 9 Chest X ray PA view

Stage	No. of patients	Normal	Chronic bronchitis	Emphysema	Chronic bronchitis + Emphysema
I	20	20	0	0	0
II	15	6	5	4	0
III	31	0	10	17	4
IV	34	0	5	24	5
Total	100	26	20	45	9

Of the 100 patients, 26 patients had normal X ray,20 patients had chronic bronchitis picture,45 patients had emphysema picture,9 patients had both chronic bronchitis and emphysema picture

Table 10 ECG Changes

ECG	I	II	III	IV
RAE	0	7	15	20
RVH	0	0	12	18
RAD	3	0	12	18
RBBB	0	3	13	10
Lead 1 sign	0	10	27	30
P wave changes	20	17	31	34

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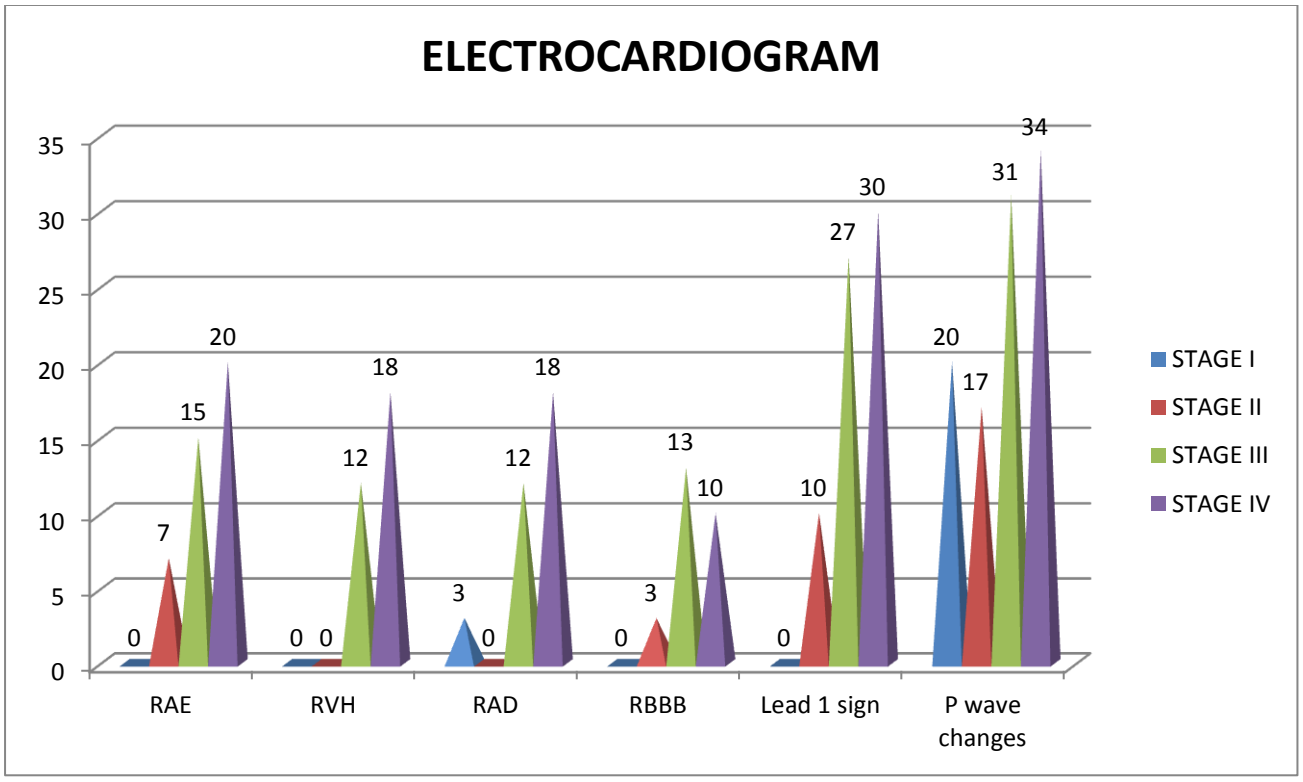
Among the total of 100 patients ,42 patients had feature of RAE,30 patients had feature of RVH,33 patients had feature of RAD,26 patients had feature of RBBB,67 patients had feature of Lead 1 sign,100 patients had feature of P wave changes.

Chart 10 ECG Changes



Among the total of 100 patients ,42 patients had feature of RAE,30 patients had feature of RVH,33 patients had feature of RAD,26 patients had feature of RBBB,67 patients had feature of Lead 1 sign,100 patients had feature of P wave changes.

Table 11 Echocardiography Changes

Stage	No. of patients	Mild PHT	Moderate PHT	Severe PHT	RV Dilatation
I	20	0	0	0	0
II	15	7	3	0	0
III	31	0	12	7	5
IV	34	0	15	9	10

Chart 11 Echocardiography Changes

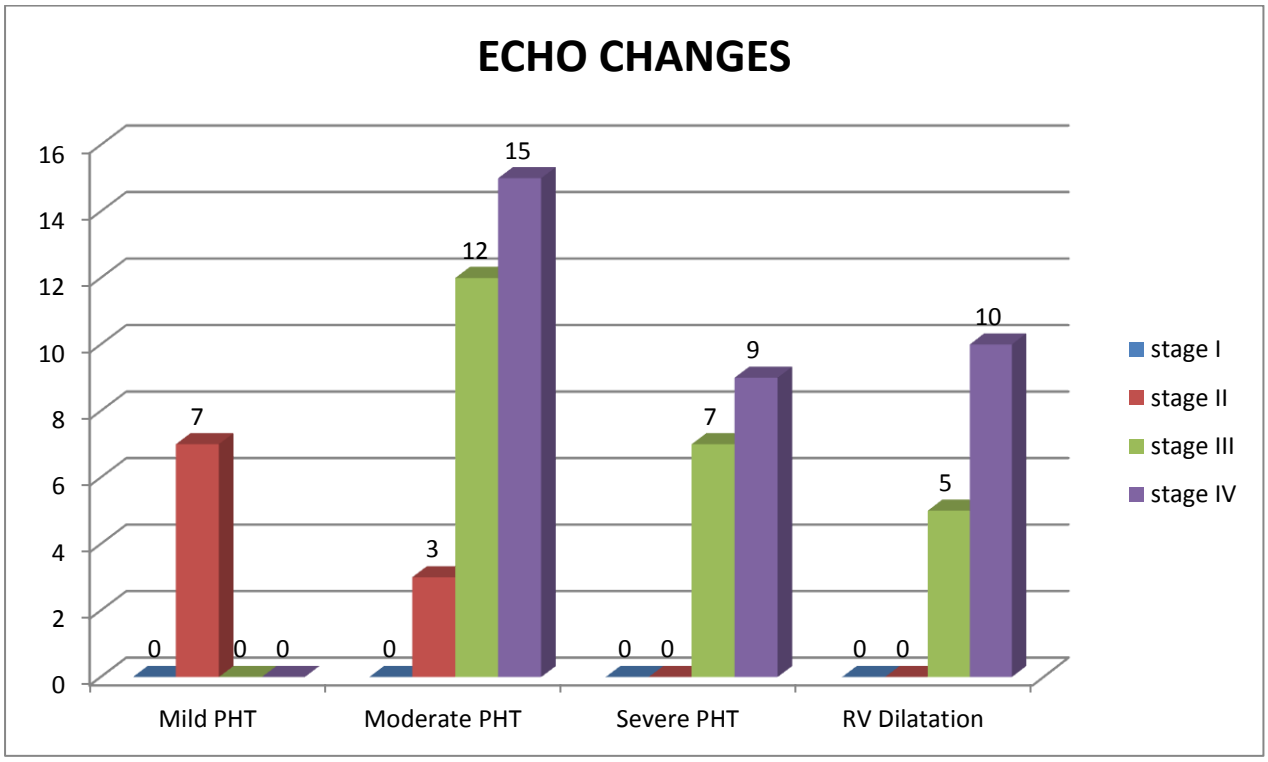


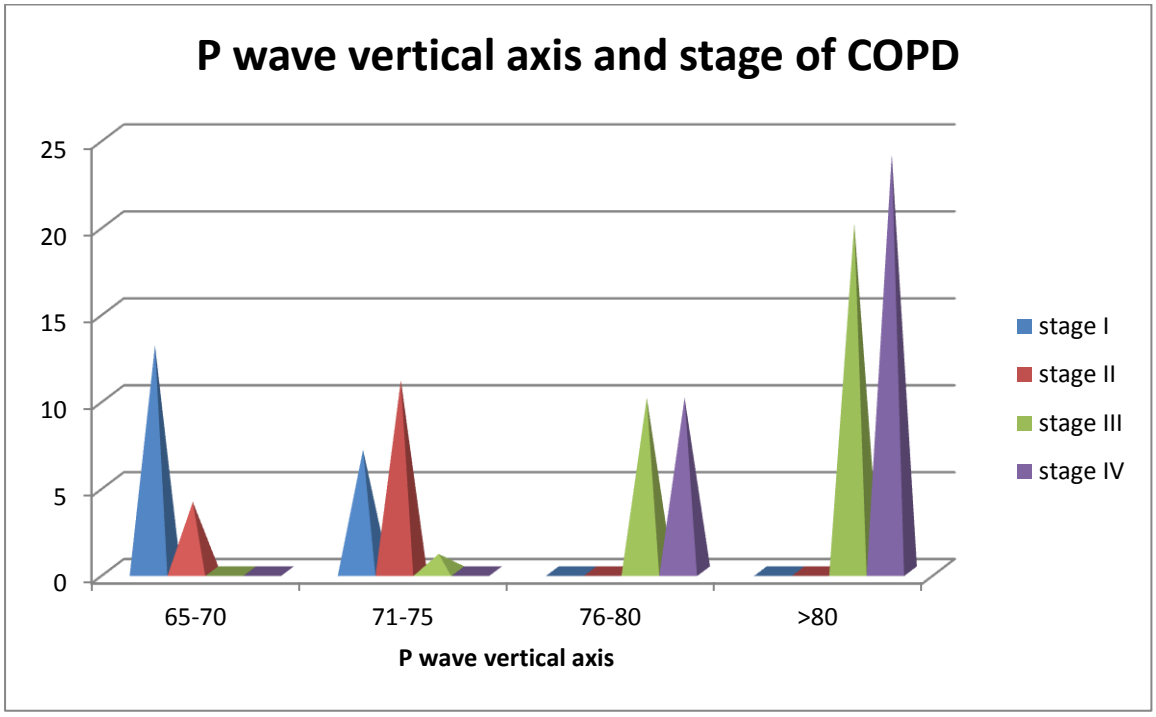
Table 12 P wave vertical axis according to stage

Stage	P wave vertical axis in degree				NO.PATIENTS
	65-70	71-75	76-80	>80	
I	13	7	0	0	20
II	4	11	0	0	15
III	0	1	10	20	31
IV	0	0	10	24	34
Total	17	19	20	44	100

Among 100 patients, 17 patients had P wave vertical axis of 65-75 degree,19 patients had p wave vertical axis of 71-75 degree,20 patients had P wave vertical axis 76-80 degree,44 had P wave vertical axis of >80 degree.

P wave vertical axis>80 degree is superior to P wave vertical axis 75 -80 degree is correlating with COPD severity and statically significant as P value is < 0.005.

Chart 12 P wave vertical axis according to stage



Among 100 patients, 17 patients had P wave vertical axis of 65-75 degree,19 patients had p wave vertical axis of 71-75 degree,20 patients had P wave vertical axis 76-80 degree,44 had P wave vertical axis of >80 degree.

P wave vertical axis>80 degree is superior to P wave vertical axis 75 -80 degree is correlating with COPD severity and statically significant as P value is < 0.005

DISCUSSION

In India, COPD is the second most common lung disorder after pulmonary tuberculosis. The disease is frequently encountered in middle aged patients and COPD has increasing public importance around the world. Estimates suggest that COPD will rise from the 6^{th} to the 3^{rd} most common cause of death worldwide by 2020. In our study total of 100 patients were studied after applying the inclusion criteria and exclusion criteria: their P wave vertical axis and severity of COPD assed by pulmonary function test.

AGE

In our study, the increasing age of the patients shows increasing stage of the diseases was found to be statistically significant with $P < 0.001$ and the correlation of age with the FEV1 of predicted value was found to statistically significant. The risk of developing the diseases has been shown to increase with age. This may be due to age related detoriation of lung function or increasing duration of smoking or sustained exposure to environmental exposure risk factor or a combination of any these, one confounding the effect of the others .

SEX

Of the 100 total 100 patients, 73 were males and 23 were females. This is because smoking, the important risk factor is common in male.

SMOKING

The study showed that there is an increasing severity of the disease as depicted by GOLD stage with the increasing in the number of pack years of smoking and it was statistically significant .also the decline in FEV1 % of predicted value also showed a negative correlation with the number of pack years of smoking which is consistent with other studies. Smoking in any form found has been regarded as the most important risk factor in almost every study for developing the disease and has been proven to have a dose – response relationship. On reviewing several studies on Indian males patients ,83.2 % were associated with smoking.

OCCUPATION

Of the total of 100, Manual labourers were 60, Dye industry workers were 9, Professional were 10, Flour mill workers were 10, Business were 4, Cotton industry workers were 7.several occupation which are associated with chemicals ,noxious gases ,minerals , dust, cotton industry have been identified as risk factors and the risk is further compounded if smoking is also present.

SYMPTOMS

In our study , all the patients had chronic cough with sputum production and a majority had shortness of breath and wheeze – the cardinal symptoms of the disease.

SIGNS

Of the 100 patients, 35 had Elevated JVP,27 patients had Pedal oedema , 75 patient had Diminished air entry, 90 patients had Rhonchi,52 patients had Crackle downward displacement of liver.

X RAY CHEST PA VIEW

Of the 100 patients, 26 patients had normal x ray,20 patients had chronic bronchitis picture,45 patients had emphysema picture,9 patients had both chronic bronchitis and emphysema picture.thses inference show that imaging could not be used to diagnose the diseases particularly in its early stages and also that two forms of the disease is not mutually exclusive as patients over time may develop features of the two.

ELECTROCARDIOGRAM

Among the total of 100 patients ,42 patients had feature of RAE,30 patients had feature of RVH,33 patients had feature of RAD,26 patients had feature of

RBBB,67 patients had feature of Lead 1 sign,100 patients had feature of P wave changes.

Among 100 patients, 17 patients had P wave vertical axis of 65-75 degree,19 patients had p wave vertical axis of 71-75 degree,20 patients had P wave vertical axis 76-80 degree,44 had P wave vertical axis of >80 degree.

P wave vertical axis>80 degree is superior to P wave vertical axis 75 -80 degree is correlating with COPD severity and statically significant as p value is < 0.005.

From this study increasing vertical axis of P wave in COPD directly correlate with diseases severity, and indirectly correlating with the FEV1 of predicted.

LIMITATIONS OF THE STUDY

The study has its own limitations

- the number of patients involved in the study “n” is small and hence generalization of the results of the study to be made with caution
- The study population involved only the patients seeking medical care in our hospital which is a tertiary care hospital and hence they may not represent general population.
- This study is a observational study. Longitudinal studies with serial assessment of the variables would be more informative.

  So, longitudinal studies with large study population and population based studies are needed to circumvent this limitation.

CONCLUSIONS

From our study we concluded that

- increasing age is associated with severity of the disease
- Males are more commonly affected then females because of smoking.
- occupational exposure to risk factors compounds the risk of developing the disease when associated with smoking
- incidence of pulmonary hypertension and right ventricular dilatation increase with increase in severity of the diseases
- p wave vertical axis is directly proportional to severity of COPD and inversely correlating with the FEV1 of predicted.

ANNEXURES

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PROFORMA

Name : **Age/Sex/Occupation:**

Presenting complaints:

H/o cough & expectoration,dyspnea,wheez. Etc.

Past history:

H/o COPD, diabeties,hypertention,tuberculosis,CVA,CAD,any chronic drug intake.

Clinical examination:

General examination:

Consciousness, Pallor, jaundice, Clubbing, Lymphadenopathy,

Vitals: PR, BP, RR, SpO2, Temperature,jvp

Systemic examination:

CVS:

RS:

Abdomen :

CNS:

LABORATORY INVESTIGATIONS

1.ECG

2.X RAY CHEST

3.ECHO

4.PULMONARY FUNCTION TEST

ABBREVIATIONS

COPD –chronic obstructive pulmonary diseases

GOLD –global initiative for chronic obstructive lung disease

ECG -electrocardiogram

FEV1 –forced expiratory volume in 1 second.

FVC – forced vital capacity

AT –anti – Trypsin

RV – residual volume

TLC –total lung capacity

FRC – functional residual capacity

ROS – reactive oxygen species

MMP- matrixmetalloprotenase

ABG – arterial blood gas

PHT – pulmonary hypertension

MAT – multifocal atrial tachycardia

CAD –coronary artery disases

NIV –non invasive ventilation

TNF alpha-tumour necrosis factor alpha

TGF BETA-transforming growth factor beta

IL – interleukin

NFKB – nuclear factor K B

LTOT – long term oxygen therapy

S.No	Name	AGE	Sex	FEV 1	p wave axis (Degree)			
					65 - 70	71- 75	76 - 80	>80
1	MOHAN	51	M	IV	-	-	-	+
2	PANDIARAJAN	53	M	IV	-	-	-	+
3	IYYAMMAL	55	F	IV	-	-	-	+
4	AYYAVU	59	M	IV	-	-	-	+
5	LAKSHMANAN	46	M	II	+	-	-	-
6	CHANDRAN	56	M	II	-	+	-	-
7	KANAGA VALLI	45	F	I	+	-	-	-
8	JAMUNA	49	F	I	+	-	-	-
9	SELVA RANI	46	F	III	-	+	-	-
10	SUMATHI	50	F	III	-	-	+	-
11	BAGHAYA LAKSHMI	60	F	I	-	+	-	-
12	MUTHU MANI	59	M	IV	-	-	+	-
13	JAYA LAKSHMI	65	F	I	-	+	-	-
14	SIVA SANKARI	46	F	II	+	-	-	-
15	BASHEER AHMEED	49	M	II	+	-	-	-
16	MANIKANDAN	47	M	I	+	-	-	-
17	IRULAYI	66	F	II	-	+	-	-
18	MARI MUTHU	77	M	III	-	-	-	+
19	SONAI MUTHU	46	M	III	-	-	-	+
20	ARJUNAN	55	M	I	+	-	-	-
21	ANGURAJ	71	M	IV	-	-	-	+
22	ESHWAR LAL	72	M	III	-	-	-	+
23	RAJAMMAL	66	F	II	-	+	-	-
24	PONAMBALAM	65	M	IV	-	-	-	+
25	RAGHAVAN	73	M	III	-	-	-	+
26	MALAIKANI	56	F	II	-	+	-	-
27	JAYAKUMAR	48	M	III	-	-	-	+
28	PREM	72	M	IV	-	-	-	+
29	RAJENDRAN	73	M	III	-	-	-	+
30	GURUVAMMAL	56	F	II	-	+	-	-
31	KUMAR	47	M	III	-	-	-	+
32	RAMESH	73	M	IV	-	-	-	+
33	PANJU	57	F	II	+	-	-	-
34	PALANIVEL	76	M	IV	-	-	-	+

35	MEENAKSHI	56	F	III	-	-	+	-
36	RANJITHAM	74	M	IV	-	-	-	+
37	ARUMUGAM	46	M	II	+	-	-	-
38	GANESAN	75	M	III	-	-	-	+
39	VIMALA	58	F	III	-	-	+	-
40	SUMATHI	65	F	III	-	-	-	+
41	KANNAN	75	M	IV	-	-	-	+
42	SANTHA RAM	47	M	I	+	-	-	-
43	VASANTHA	59	F	III	-	-	-	+
44	INDRA	55	F	IV	-	-	+	-
45	KASIRAJAN	49	M	II	-	+	-	-
46	THAVAMANI	65	F	III	-	-	+	-
47	MYTHILI	53	F	IV	-	-	+	-
48	VASUDEVAN	68	M	I	+	-	-	-
49	NARAYANAN	74	M	III	-	-	-	+
50	KALAISELVI	65	F	III	-	-	+	-
51	SUBRAMANI	56	M	II	-	+	-	-
52	SIVAGAMI	66	F	IV	-	-	-	+
53	SATHYA	73	F	IV	-	-	-	+
54	PRIYA	75	F	IV	-	-	-	+
55	SARAVANAN	48	M	III	-	-	+	-
56	SAHADEVAN	64	M	IV	-	-	-	+
57	PREM	59	M	I	-	+	-	-
58	KUMAR	66	M	II	-	+	-	-
59	SIVAKUMAR	55	M	III	-	-	-	+
60	JOTHI	66	F	IV	-	-	+	-
61	JEYABALAN	65	M	I	+	-	-	-
62	ATHI LAKSHMI	69	F	IV	-	-	-	+
63	RAVI MUTHU	60	M	III	-	-	-	+
64	RAMU	70	M	I	+	-	-	-
65	RAMESH KUMAR	67	M	II	-	+	-	-
66	RAJESH	65	M	III	-	-	-	+
67	RAJESHWRI	73	F	IV	-	-	+	-
68	PANNER SELVAM	78	M	IV	-	-	-	+
69	PACHAYAPPAN	59	M	III	-	-	-	+
70	PICHAI MANI	55	M	I	-	+	-	-
71	RAJU	63	M	IV	-	-	-	+
72	ULAKANATHAN	76	M	III	-	-	-	+
73	RAMU	59	M	I	-	+	-	-
74	KATHIR	69	M	II	-	+	-	-
75	VANKATESH	65	M	I	+	-	-	-
76	SRINIVASAN	47	M	III	-	-	+	-
77	SOMASUNTHARAM	54	M	I	-	+	-	-
78	NAATARAJAN	62	M	IV	-	-	-	+
79	MURALITHARAN	56	M	III	-	-	-	+
80	PRIYA	78	F	IV	-	-	+	-
81	SUNTHARI	73	F	IV	-	-	-	+
82	DHANALAKSHMI	75	F	IV	-	-	-	+
83	DENANATHAN	45	M	III	-	-	+	-

84	VINOTH KUMAR	77	M	IV	-	-	-	+
85	SENTHIL	55	M	I	+	-	-	-
86	AJITH	75	M	III	-	-	-	+
87	PRABU	59	M	IV	-	-	-	+
88	SELVARANI	54	F	I	-	+	-	-
89	KALAI SELVAN	79	M	IV	-	-	-	+
90	LARANCE	67	M	III	-	-	-	+
91	AJAI	70	M	IV	-	-	-	+
92	MOHAMAD JINNA	59	M	I	+	-	-	-
93	SANMUGAM	66	M	III	-	-	-	+
94	MURUGAN	58	M	I	+	-	-	-
95	MATHAN	57	M	IV	-	-	-	+
96	GOVINTHAN	49	M	III	-	-	+	-
97	SIVASITHAM BARAM	58	M	IV	-	-	-	+
98	HAHAMOD	70	M	I	+	-	-	-
99	ARUBI PRASATH	56	M	IV	-	-	-	+
100	ANADTH	46	M	III	-	-	+	-

Ref.No.6506/E1/5/2014

Madurai Medical College,
Maduai -20. Dated: 07 .2014.

Institutional Review Board/Independent Ethics Committee
Capt.Dr.B.Santhakumar,MD (FM). deanmdu@gmail.com
Dean, Madurai Medical College &
Government Rajaji Hospital, Madurai 625 020 . **Convenor**

Sub: Establishment – Madurai Medical College, Madurai-20 – Ethics Committee Meeting – Meeting Minutes - for July 2014 – Approved list – reg.

The Ethics Committee meeting of the Madurai Medical College, Madurai was held on 22nd July 2014 at 10.00 Am to 12.00 Noon at Anaesthesia Seminar Hall at Govt. Rajaji Hospital, Madurai . The following members of the Ethics Committee have attended the meeting.

1.Dr.V.Nagarajan,M.D.,D.M(Neuro) Ph: 0452-2629629 Cell No.9843052029 nag9999@gmail.com.	Professor of Neurology (Retired) D.No.72, Vakkil New Street, Simmakkal, Madurai -1	Chairman
2.Dr.Mohan Prasad, MS.M.Ch. Cell.No.9843050822 (Oncology) drbkcmp@gmail.com	Professor & H.O.D of Surgical Oncology (Retired) D.No.32, West Avani Moola Street, Madurai.-1	Member Secretary
3. Dr.L.Santhanalakshmi, MD (Physiology) Cell No.9842593412 dr.l.santhanalakshmi@gmail.com.	Vice Principal, Prof. & H.O.D. Institute of Physiology Madurai Medical College	Member
4.Dr.K.Parameswari, MD(Pharmacology) Cell No.9994026056 drparameswari@yahoo.com.	Director of Pharmacology Madurai Medical College.	Member
5.Dr.S.Vadivel Murugan, MD., (Gen.Medicine) Cell No.9566543048 svadivelmurugan_2007@rediffmail.com.	Professor & H.O.D of Medicine Madurai Medical College	Member
6.Dr.A.Sankaramahalingam, MS., (Gen. Surgery) Cell.No.9443367312 chandrahospitalmdu@gmail.com	Professor & H.O.D. Surgery Madurai Medical College.	Member
7.Mrs.Mercy Immaculate Rubalatha, M.A., Med., Cell.No.9367792650 lathadevadoss86@gmail.com	50/5, Corporation Officer's Quarters, Gandhi Museum Road, Thamukam, Madurai-20.	Member
8.Thiru.Pala.Ramasamy, B.A.,B.L., Cell.No.9842165127 palaramasamy2011@gmail.com	Advocate, D.No.72,Palam Station Road, Sellur, Madurai-20.	Member
9.Thiru.P.K.M.Chelliah, B.A., Cell No.9894349599 pkmandco@gmail.com	Businessman, 21 Jawahar Street, Gandhi Nagar, Madurai-20.	Member

The following project was approved by the committee

Name of the PG Student	Course	Name of the Project	Remarks
Dr.Srinivasan S.S dr_srini@ymail.com	PG in MD (General Medicine) Madurai Medical College & Rajaji Hospital, Madurai	Study of Correlation between P wave vertical axis and COPD Severity by pulmonary function test	Approved

Please note that the investigator should adhere the following: She/He should get a detailed informed consent from the patients/participants and maintain it confidentially.

1. She/He should carry out the work without detrimental to regular activities as well as without extra expenditure to the institution or to Government.
2. She/He should inform the institution Ethical Committee, in case of any change of study procedure, site and investigation or guide.
3. She/He should not deviate the area of the work for which applied for Ethical clearance.
   She/He should inform the IEC immediately, in case of any adverse events or serious adverse reactions.
4. She/He should abide to the rules and regulations of the institution.
5. She/He should complete the work within the specific period and if any extension of time is required He/She should apply for permission again and do the work.
6. She/He should submit the summary of the work to the Ethical Committee on completion of the work.
7. She/He should not claim any funds from the institution while doing the work or on completion.
8. She/He should understand that the members of IEC have the right to monitor the work with prior intimation.

Member Secretary
Ethical Committee

Chairman
Ethical committee

31.7.14

DEAN/Convenor
Madurai Medical College & Govt.
Rajaji Hospital, Madurai.

To
The above Applicant
-thro. Head of the Department concerned

STUDY OF CORRELATION BETWEEN P WAVE VERTICAL AXIS AND COPD SEVERITY BY PULMONARY FUNCTION TEST

DISSERTATION SUBMITTED FOR
M.D GENERAL MEDICINE
BRANCH –I
APRIL 2015

THE TAMILNADU
DR.M.G.R. MEDICAL UNIVERSITY
CHENNAI, TAMILNADU, INDIA

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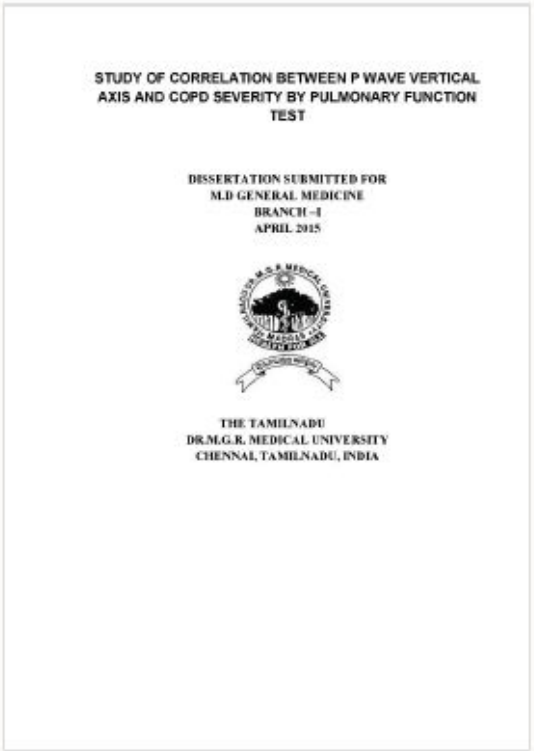

STUDY OF CORRELATION BETWEEN P WAVE VERTICAL AXIS AND COPD SEVERITY BY PULMONARY FUNCTION TEST

DISSERTATION SUBMITTED FOR
M.D GENERAL MEDICINE
BRANCH – I
APRIL 2015

THE TAMILNADU
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CHENNAI, TAMILNADU, INDIA